Renal Resistive Index and Cardiovascular and Renal Outcomes in Essential Hypertension

Yohei Doi, Yoshio Iwashima, Fumiki Yoshihara, Kei Kamide, Shin-ichirou Hayashi, Yoshinori Kubota, Satoko Nakamura, Takeshi Horio, Yuhei Kawano

Abstract—Increased renal resistive index (RI) measured using Doppler ultrasonography has been shown to correlate with the degree of renal impairment in hypertensive patients. We investigated the prognostic role of RI in cardiovascular and renal outcomes. A total of 426 essential hypertensive subjects (mean age, 63 years; 50% female) with no previous cardiovascular disease were included in this study. Renal segmental arterial RI was measured by duplex Doppler ultrasonography. During follow-up (mean, 3.1 years), 57 participants developed the primary composite end points including cardiovascular and renal outcomes. In multivariate Cox regression analysis, RI was an independent predictor of worse outcome in total subjects (hazard ratio, 1.71 for 1 SD increase), as well as in patients with estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m² (hazard ratio, 2.11 for 1 SD increase; \(P<0.01\), respectively). When divided into 4 groups based on the respective sex-specific median levels of RI in the eGFR ≥60 and eGFR <60 mL/min per 1.73 m² groups, the group with eGFR <60 and high RI (male ≥0.73, female ≥0.72) had a significantly poorer event-free survival rate (\(\chi^2=126.4; P<0.01\)), and the adjusted hazard ratio by multivariate Cox regression analysis was 9.58 (95% CI, 3.26–32.89; \(P<0.01\)). In conclusion, impairment of renal hemodynamics evaluated by increased RI is associated with an increased risk of primary composite end points, and the combination of high RI and low eGFR is a powerful predictor of these diseases in essential hypertension. In hypertensive patients with chronic kidney disease, RI evaluation may complement predictors of cardiovascular and renal outcomes. (Hypertension. 2012; 60:770-777.)

Key Words: cardiovascular disease ■ renal hemodynamics ■ ultrasonography ■ hypertension ■ predictor

In the past few years, there has been growing attention to markers of subclinical renal damage because they provide an accurate prediction of global cardiovascular outcome. Renal Doppler sonography permits noninvasive assessment of intrarenal hemodynamics in addition to evaluation of anatomic information. Intrarenal arterial waveforms recorded by Doppler ultrasonography have been widely used to evaluate renal dysfunction. Previous studies have explored the capacity of resistive index (RI) calculated from blood flow velocity in vessels to predict the progression of renal function in patients with hypertension, diabetes mellitus, or chronic nephropathy. In addition, histological studies demonstrated that RI not only reflects changes in intrarenal perfusion and renovascular resistance but was increased in several pathological conditions, such as renal atherosclerosis and tubulointerstitial damage. In previous studies, the prognostic value of RI was examined only in chronic nephropathy, elderly, or heart failure patients; however, the results obtained were inconsistent. Thus, the status of RI as an independent cardiovascular risk marker remains to be elucidated. Estimated glomerular filtration rate (eGFR), which is a measure of the kidneys' ability to filter blood, has proven to be a predictor of cardiovascular disease in the general population, as well as in hypertensive patients. Evaluation of renal RI in addition to eGFR may help to assess not only renal function but also intrarenal hemodynamics, as well as intrarenal vascular resistance, and thus may provide clinically sensitive prognostic information in patients with essential hypertension. However, the additional predictive value of these abnormalities has not been elucidated. Therefore, this study was undertaken to identify the clinical significance of RI, in middle-aged and elderly essential hypertensive subjects, to determine its impact on cardiovascular and renal outcome. In addition, we further examined whether assessment of RI adds to the prognostic information provided by eGFR.

Methods

The study protocol was approved by the ethics committee of our institution. All of the subjects enrolled in this study were Japanese and gave informed consent to participate in this study.

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Study Subjects
This study enrolled 426 (213 female) essential hypertensive patients in normal sinus rhythm who had good quality renal sonographic recordings. The patients were consecutively recruited for this study from among those attending the outpatient clinic. In our laboratory (the National Cerebral and Cardiovascular Center), all of the hypertensive patients attended the renal sonographic laboratory, and renal sonographic data were routinely collected. Exclusion criteria included ischemic heart disease, acute coronary syndrome, congestive heart failure (New York Heart Association class II or greater), valvular heart disease including moderate or severe aortic or mitral regurgitation, old cerebral infarction, history of transient ischemic attack, secondary hypertension, renal artery stenosis, heart rate >100 bpm, low ejection fraction (<45%), or receiving hemodialysis or erythropoietin therapy. Hypertension was defined as systolic blood pressure (BP) of ≥140 mm Hg or diastolic BP of ≥90 mm Hg on multiple measurements during ≥2 separate office visits or receiving antihypertensive treatment. Diabetes mellitus was defined according to the American Diabetes Association criteria. Smoking status was determined by interview and defined as never smoker, former smoker (smoked ≥100 cigarettes in his/her lifetime, but did not smoke for >1 year at the time of interview), and current smoker.

Baseline Clinical Characteristics
After fasting overnight, BP was measured with an appropriate arm cuff and a mercury column sphygmomanometer on the left arm after a resting period of ≥10 minutes in the sitting posture. After BP measurement, venous blood sampling from all of the subjects was performed. Height and body weight were measured, and body mass index was calculated. The following parameters were also determined: total cholesterol, triglycerides, high-density lipoprotein cholesterol, fasting glucose, hemoglobin A1c, creatinine, and high-sensitive C reactive protein. eGFR was calculated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation in milliliters per minute per 1.73 meters squared. Urinary albumin excretion was evaluated in each patient by measuring the albumin:creatinine ratio (ACR) in 3 consecutive first morning samples. The mean of 3 urine collections was taken as ACR for each patient (see the online-only Data Supplement).

Renal Ultrasonography and Doppler Studies
Ultrasonographic examinations were performed using duplex Dopper sonography; the ultrasonographic procedure that we adopted has been described previously (see the online-only Data Supplement). Peak systolic velocity (PSV) and minimum end-diastolic velocity (EDV) were determined using the angle correction menu of the apparatus, and RI was defined as follows: (PSV–EDV)/PSV. All of the velocities were determined for each segmental artery and averaged to obtain the mean value for each patient. All of the measurements were performed by 2 experienced physicians (K.K. and Y.I.), who were blinded to the clinical data of the subjects. The reproducibility of RI measurements by 2 investigators was assessed in a subgroup of 20 patients, in whom measurements were performed within 1 hour by both investigators in a blinded fashion. The intraobserver and interobserver coefficients of variation for the measurements were 2.7% and 3.2%.

Cardiovascular and Renal Outcomes
For survival analysis, observation began on the day of renal ultrasonography with verified updates through September 2011. All of the subjects were followed at the National Cerebral and Cardiovascular Center and treated by implementation of standard lifestyle and pharmacological measures. All of the participants were periodically referred to our institution for BP control and other diagnostic procedures. The primary end point of this study was first occurrence of composite of cardiovascular and renal events including all-cause death, myocardial infarction, stroke, congestive heart failure requiring hospitalization, aortic dissection, and end-stage renal failure requiring regular hemodialysis (see the online-only Data Supple-

Statistical Analysis
Summary statistics are presented as mean (±SD) for continuous variables and percentages for categorical variables unless otherwise specified. The subjects were divided into 2 groups according to whether RI was below or above the median value for each sex, and then the significance of any differences between groups was evaluated using unpaired t test. Event-free survival analysis was performed using the Kaplan-Meier method to plot the cumulative incidence of primary composite end points according to median value of RI for each sex, and the groups were compared by Mantel log-rank test. Cox proportional hazard analysis was used to examine the association between variables and the cumulative incidence of primary composite end points in crude and multivariate models, after accounting for relevant variables using a P value of <0.05 as the selection criterion. These effects were measured by the hazard ratio (HR) and 95% CI based on Cox regression models.

The relationships between RI and various parameters were assessed using univariate linear regression analysis and Pearson correlation coefficient. We next divided the participants into 2 groups by eGFR of 60 mL/min per 1.73 m² and then stratified the participants into 4 groups according to the respective sex-specific median values of RI in participants with eGFR ≥60 or <60. One-way ANOVA with Scheffe multiple comparison posttest was used to analyze data among the 4 groups. Event-free survival analysis was performed using the Kaplan-Meier method to plot the cumulative incidence of primary composite end points. The relative risk of primary composite end points in Cox proportional hazard analysis was assessed in crude and multivariate models, and the cumulative incidence was calculated using the group with high eGFR and low RI as a reference for each. All of the P values were 2 sided, and those <0.05 were considered statistically significant. All of the calculations were performed using a standard statistical package (SPSS, version 17.0; SPSS Inc, Chicago, IL).

Results

Baseline Characteristics and Cardiovascular and Renal Outcomes
Baseline clinical characteristics of the study subjects are listed in Table 1. Mean age was 63.1 ± 13.5 years (range, 20–85 years); 50% were female, and body mass index was 24.7 ± 4.3 kg/m². Diabetes mellitus was present in 28.9% of the subjects, and 43.2% were former or current smokers.

Among the 426 subjects, 57 (13.4%; 19 women) developed the primary composite end points during a mean follow-up of 3.1 ± 2.1 years. Specifically, there were 21 patients with nonfatal congestive heart failure, 12 with stroke, 3 with myocardial infarction, 4 with aortic dissection, 11 requiring regular hemodialysis therapy, and 6 patients died. No patient underwent kidney transplantation.

RI was significantly higher in patients who developed the primary composite end points during the follow-up period than in event-free subjects (0.77 ± 0.10 versus 0.66 ± 0.08; P < 0.01). Specifically, RI was significantly higher in both patients who developed cardiovascular end points including nonfatal congestive heart failure, stroke, myocardial infarction, aortic dissection, and death (0.76 ± 0.10 versus 0.66 ± 0.08), as well as end-stage renal failure patients requiring regular hemodialysis therapy (0.81 ± 0.06 versus...
Table 1. Baseline Clinical Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>RI Less Than Median (Male &lt; 0.65, Female &lt; 0.68)</th>
<th>RI Median or More (Male ≥ 0.65, Female ≥ 0.68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>426</td>
<td>214</td>
<td>212</td>
</tr>
<tr>
<td>Male, %</td>
<td>50.0</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.1 ± 13.5</td>
<td>56.1 ± 13.4</td>
<td>70.2 ± 9.3†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.7 ± 4.3</td>
<td>24.9 ± 4.4</td>
<td>24.6 ± 4.1</td>
</tr>
<tr>
<td>Former or current smokers, %</td>
<td>43.2</td>
<td>43.5</td>
<td>42.9</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>15.5 ± 12.0</td>
<td>13.1 ± 11.5</td>
<td>17.9 ± 12.0†</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>28.9</td>
<td>20.6</td>
<td>37.3†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>141 ± 17</td>
<td>140 ± 18</td>
<td>142 ± 17</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 ± 12</td>
<td>84 ± 12</td>
<td>75 ± 9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67 ± 9</td>
<td>68 ± 8</td>
<td>65 ± 9†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.07 ± 1.01</td>
<td>4.97 ± 1.01</td>
<td>5.18 ± 0.99†</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.53 ± 1.08</td>
<td>1.55 ± 1.07</td>
<td>1.50 ± 1.09</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.33 ± 0.39</td>
<td>1.38 ± 0.40</td>
<td>1.28 ± 0.37†</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>6.01 ± 1.81</td>
<td>5.91 ± 1.90</td>
<td>6.12 ± 1.72</td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>5.92 ± 1.21</td>
<td>5.81 ± 1.07</td>
<td>6.02 ± 1.32</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>96.4 ± 84.6</td>
<td>72.4 ± 27.6</td>
<td>120.7 ± 111.7</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>66.1 ± 23.9</td>
<td>75.9 ± 17.7</td>
<td>56.3 ± 25.4†</td>
</tr>
<tr>
<td>ACR, mg/g creatinine, median (IQR)</td>
<td>14.8 (6.3–118.2)</td>
<td>9.3 (5.0–33.4)</td>
<td>25.6 (8.6–446.5)†</td>
</tr>
<tr>
<td>Hs-CRP, mg/L, median (IQR)</td>
<td>0.80 (0.40–1.68)</td>
<td>0.70 (0.35–1.50)</td>
<td>0.90 (0.40–1.80)</td>
</tr>
<tr>
<td>Right kidney, cm</td>
<td>10.3 ± 1.0</td>
<td>10.4 ± 0.9</td>
<td>10.2 ± 1.1†</td>
</tr>
<tr>
<td>Left kidney, cm</td>
<td>10.3 ± 1.0</td>
<td>10.5 ± 1.0</td>
<td>10.1 ± 1.1†</td>
</tr>
<tr>
<td>Renal RI</td>
<td>0.67 ± 0.09</td>
<td>0.60 ± 0.05</td>
<td>0.75 ± 0.06†</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>71.8</td>
<td>63.4</td>
<td>80.2†</td>
</tr>
<tr>
<td>β-blocker</td>
<td>25.9</td>
<td>21.1</td>
<td>30.7*</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>58.1</td>
<td>52.1</td>
<td>64.2*</td>
</tr>
<tr>
<td>Diuretic</td>
<td>29.4</td>
<td>23.0</td>
<td>35.9†</td>
</tr>
<tr>
<td>Primary composite end points, n</td>
<td>57</td>
<td>8</td>
<td>49†</td>
</tr>
<tr>
<td>Cardiovascular events, n</td>
<td>46</td>
<td>7</td>
<td>39†</td>
</tr>
<tr>
<td>ESRF requiring hemodialysis, n</td>
<td>11</td>
<td>1</td>
<td>10†</td>
</tr>
</tbody>
</table>

Values are mean ± SD or frequency (%). IQR is 25th to 75th percentile. RI indicates resistive index; HDL cholesterol, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACR, albumin:creatinine ratio; Hs-CRP, high-sensitive C reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESRF, end-stage renal failure; IQR, interquartile range.

*P < 0.05 vs RI less than median.
†P < 0.01 vs RI less than median.

0.66 ± 0.08; P < 0.01, respectively). Because RI was significantly lower in male than in female participants (0.66 ± 0.10 versus 0.69 ± 0.08; P < 0.01), different median values for men and women were used to separate the high and low RI groups (male, < 0.65; female, < 0.68). The group with high RI showed significantly older age, longer duration of hypertension, lower heart rate, higher prevalence of diabetes mellitus, higher total cholesterol, lower high-density lipoprotein cholesterol, lower eGFR, and higher ACR than that with low RI (Table 1).

Relation of RI to Primary Composite End Points

Life table analysis of the primary composite end points throughout the follow-up period in the 2 groups based on RI is plotted in Figure 1. These curves illustrate the significantly poorer event-free survival in the group with high RI. A univariate Cox proportional-hazard model showed that RI (HR, 1.81 for each 1 SD [ie, 0.10 for male and 0.08 for female] increase [95% CI, 1.45–2.27]; P < 0.01) was a significant predictor of the primary composite end points. Other variables in this study that significantly predicted the primary end points included age (HR, 2.01 for each 1 SD [ie, 13.5 years] increase [95% CI, 1.44–2.87]; P < 0.01), sex (HR, 2.25 for male [95% CI, 1.32–3.99]; P < 0.01), systolic BP (HR, 1.36 for each 1 SD [ie, 17 mm Hg] increase [95% CI, 1.06–1.71]; P = 0.02), diabetes mellitus (HR, 2.50 for yes [95% CI, 1.48–4.22]; P < 0.01), high-density lipoprotein cholesterol (HR, 0.60 for each 1 SD [ie, 0.39 for male and 0.37 mmol/L for female] increase [95% CI, 0.44–0.81]; P < 0.01), eGFR (HR, 0.27 for each 1 SD [ie, 19.1 mL/min per
1.73 m²) increase [95% CI, 0.20–0.35]; P < 0.01). ACR (HR, 1.68 for each 1 SD [ie, 893.0 for male and 954.7 mg/g of creatinine for female] increase [95% CI, 1.49–1.86]; P < 0.01), and left kidney-size (HR, 0.59 for each 1 SD [ie, 1.0 cm for male and female] increase [95% CI, 0.49–0.73]; P < 0.01). Log-transformed ACR, as well as left kidney size, was significantly associated with RI (ACR: male, r = 0.53, female, r = 0.45; kidney-size: male, r = –0.33, female, r = –0.26) and eGFR (ACR: male, r = –0.65, female, r = –0.60; kidney-size: male, r = 0.52, female, r = 0.42; P < 0.01, respectively), and, thus, multivariate Cox regression analysis in which ACR and kidney size were not included in the same model was first performed. After adjusting for other risk factors (age, sex, systolic BP, diabetes mellitus, high-density lipoprotein cholesterol, and eGFR) in multivariate Cox regression analysis, independence of RI (HR, 1.71 for each 1 SD increase [95% CI, 1.19–2.56]; P < 0.01) as a predictor of the primary composite end points was found. The further addition of ACR, left kidney size, and antihypertensive medication to the model did not meaningfully influence the results (HR, 1.72 for each 1 SD increase [95% CI, 1.18–2.59]; P < 0.01).

We next repeated our analysis for the 133 patients with eGFR < 60 mL/min per 1.73 m². In this analysis, 44 primary composite end point events (33.1%, 14 female) occurred during the follow-up period. A univariate Cox proportional hazard model showed that RI was a significant predictor of the primary composite end points (HR, 2.12 for 1 SD [ie, 0.10 for male and 0.09 for female] increase [95% CI, 1.57–2.89]; P < 0.01). Other variables in this subgroup that significantly predicted the primary composite end points included sex (HR, 1.77 for male [95% CI, 1.10–2.97]; P < 0.05) and eGFR (HR, 0.28 for 1 SD [ie, 16.64 mL/min per 1.73 m²] increase [95% CI, 0.18–0.41]; P < 0.01). The results of multivariate Cox regression analysis including sex and eGFR showed that RI (HR, 2.11 for 1 SD increase [95% CI, 1.44–3.16]; P < 0.01) was an independent predictor of the composite end points.

Joint Effect of RI and eGFR on Primary Composite End Points

In both total subjects (male: r = –0.62, female: r = –0.55) and the subgroup with eGFR < 60 mL/min per 1.73 m² (male: r = –0.39, female: r = –0.54), RI was significantly associated with eGFR (P < 0.01, respectively). To assess the combined effects of eGFR and RI, therefore, we constructed survival curves after dividing the subjects into 2 groups by eGFR of 60 mL/min per 1.73 m² and then stratified the subjects into 4 groups according to the sex-specific median values of RI in the group with eGFR ≥ 60 (RI, 0.62 for male and 0.67 for female) and that with eGFR < 60 (RI, 0.73 for male and 0.72 for female). As a result, the subjects were divided into 4 groups as follows: eGFR ≥ 60 and low RI, eGFR ≥ 60 and high RI, eGFR < 60 and low RI, and eGFR < 60 and high RI. The baseline clinical and biochemical characteristics of the study subjects are shown in Table 2. Compared with the group with eGFR ≥ 60 and low RI, the group with eGFR < 60 and high RI showed an increased risk of cardiovascular morbidity, such as significantly higher age, longer duration of hypertension, higher prevalence of diabetes mellitus, lower high-density lipoprotein cholesterol, and higher ACR. Life table analyses of the primary composite end points throughout the follow-up period according to the 4 groups of eGFR and RI are plotted in Figure 2. These curves illustrate the significantly poorer event-free survival in the group with eGFR < 60 and high RI. We next performed Cox regression analysis to examine whether the influence of a low eGFR and high RI on the primary composite end points was independent of other risk factors (Table 3). The risk of the primary composite end points was significantly higher in the group with eGFR < 60 and high RI compared with that in the group with eGFR ≥ 60 and low RI (HR, 19.8). In multivariate Cox regression analysis including age, sex, systolic BP, diabetes mellitus, and high-density lipoprotein cholesterol, the combination of eGFR < 60 and high RI was an independent predictor of the primary composite end points (HR, 9.58). The relative risk in the eGFR < 60 and high RI group remained highly significant even after including ACR, left kidney size, and antihypertensive medication in the model (HR, 5.64 [95% CI, 3.18–12.16]; P < 0.01). Even when the group with eGFR < 60 and low RI was used as a reference, the group with eGFR < 60 and high RI had a significantly higher risk of the primary composite end points in univariate Cox regression analysis (HR, 5.48 [95% CI, 2.74–12.16]; P < 0.01) and in a multivariate model (HR, 4.78 [95% CI, 2.19–11.65]; P < 0.01).

In addition, the influence of the combination of renal RI and eGFR on outcomes was also examined by dividing the 4 groups according to eGFR of 45 mL/min per 1.73 m² and the sex-specific median values of RI in the group with eGFR ≥ 45 mL/min per 1.73 m² (RI, 0.63 for male and 0.67 for female) and that with eGFR < 45 mL/min per 1.73 m² (RI, 0.75 for male and 0.77 for female); that is, eGFR ≥ 45 and low RI (n = 172), eGFR ≥ 45 and high RI (n = 168), eGFR < 45 and low RI (n = 43), and eGFR < 45 and high RI (n = 43). The relative risks of the primary composite end points in the eGFR ≥ 45 and low RI, eGFR ≥ 45 and high RI, eGFR < 45 and low RI, and eGFR < 45 and high RI were 4.64 (95% CI, 2.12–10.08), 4.64 (95% CI, 2.12–10.08), 4.64 (95% CI, 2.12–10.08), and 4.64 (95% CI, 2.12–10.08), respectively.
Discussion

The present study demonstrated that the relationship between high RI and cardiovascular and renal outcomes is significant and persisted after multivariate Cox regression analysis, including traditional risk factors. Moreover, even in the subgroup with eGFR < 60 mL/min per 1.73 m², high RI was a significant predictor of the primary composite end points. The combination of high RI and low eGFR was a powerful independent predictor of worse outcome.

Our results showed that a high RI is independently associated with cardiovascular and renal outcomes and suggest that assessment of RI by ultrasonography, a simple method of

and high RI groups were 1.0 (reference), 2.32 (95% CI, 0.86–7.28), 8.88 (95% CI, 3.29–27.92), and 28.03 (95% CI, 11.77–82.66) in univariate Cox regression analysis and 1.0 (reference), 1.29 (95% CI, 0.44–4.37), 4.97 (95% CI, 1.70–16.60), and 11.45 (95% CI, 3.97–38.96) in multivariate Cox regression analysis, respectively. Even when the group with eGFR < 45 and low RI was used as a reference, the independent predictive value of eGFR < 45 and high RI for primary composite end points was also confirmed in univariate Cox regression analysis (HR, 3.16 [95% CI, 1.64–6.47]; P<0.01) and in a multivariate model (HR, 2.30 [95% CI, 1.10–5.14]; P=0.02).
assessing intrarenal hemodynamics,\textsuperscript{2,3} is useful for predicting the risk of these diseases in essential hypertension. Furthermore, even when analysis was restricted to the subgroup with eGFR <60 mL/min per 1.73 m\textsuperscript{2}, which is defined as chronic kidney disease,\textsuperscript{24} the independent role of RI in outcomes was maintained. These findings were partially in agreement with those from previous studies on high-risk patients with chronic nephropathy,\textsuperscript{2} transplant renal allograft,\textsuperscript{22} or heart failure\textsuperscript{12} and extend the predictive role of renal hemodynamic abnormalities to essential hypertensive patients. These findings corroborate the hypothesis that the impact of RI on cardiovascular and renal risk is marked and that identifying renal hemodynamic abnormalities is useful for predicting cardiovascular and renal outcomes, especially in hypertensive patients with chronic kidney disease. The precise mechanisms by which the risk for these diseases becomes higher with increasing RI are unclear; however, there are several hypothetical mechanisms. Previous historical studies have also demonstrated that RI correlates not only with renal function\textsuperscript{25} but also with renal histopathologic findings, such as renal atherosclerosis or tubulointerstitial damage.\textsuperscript{8–10} In renal allograft patients, RI of the transplanted kidney significantly correlates with the age of the recipient but not with the age of the kidney,\textsuperscript{26} suggesting that extrarenal factors, such as stiffness of the prerenal vessels, for example, the aorta, have a major effect on renal Doppler indices. Vascular resistance and especially vascular compliance, which is the rate of change of volume of a vessel as a function of pressure, are the main predictors of renal RI.\textsuperscript{2} Other studies have investigated the relationship between RI of transplanted kidneys and parameters of cardiovascular disease and found a significant correlation of renal RI with ankle-brachial BP index\textsuperscript{27} and carotid-femoral pulse wave velocity,\textsuperscript{28} without any correlation with creatinine clearance of the graft. Other studies also found that, in essential hypertension, RI was associated with ambulatory arterial stiffness index\textsuperscript{29} or central pulse pressure and aortic stiffness.\textsuperscript{30} Therefore, renal RI should be considered as a marker of systemic atherosclerotic vessel damage rather than a specific marker of renal damage.

It is noteworthy that patients with both decreased eGFR and increased RI had a significant burden of cardiovascular risk factors and a higher risk of the primary composite end points as compared with those with either isolated decreased eGFR or increased RI. The Kidney Disease: Improving Global Outcomes foundation has recently modified the classification of stage 3 chronic kidney disease by subdivision into 2 stages at eGFR of 45 mL/min per 1.73 m\textsuperscript{2},\textsuperscript{31} and, thus, we repeated analysis by categorizing our study group according to eGFR of 45 mL/min per 1.73 m\textsuperscript{2} and found increased risk in those patients with eGFR <45 mL/min per 1.73 m\textsuperscript{2} and high RI. These findings suggest that combined screening for eGFR and intrarenal hemodynamics might improve their combined predictive power, especially in hypertensive patients with chronic kidney disease. On the other hand, in the group with eGFR ≥60 mL/min per 1.73 m\textsuperscript{2}, the risk of outcomes did not become higher with increasing RI. Therefore, once a patient is diagnosed with chronic kidney disease, RI appears to be a useful marker to estimate their cardiovas-

\[ \text{eGFR} \geq 60/ \text{Low RI} \]
\[ \text{eGFR} < 60/ \text{Low RI} \]
\[ \text{eGFR} < 60/ \text{High RI} \]
\[ \text{eGFR} \geq 60/ \text{High RI} \]
cular or renal risk. A cluster of traditional cardiovascular risk factors, such as older age, severity and duration of hypertension, and worse dyslipidemia, was observed in the subgroup with lower eGFR and higher RI; however, the risk of primary composite end points remained significantly worse even after adjusting for these confounders. Although both eGFR and increased RI reflect renal dysfunction, the pathophysiological mechanisms leading to these abnormalities may be, at least in part, different. It has been shown that a decrease in eGFR is associated with oxidative stress, subclinical inflammation, increased homocysteine, insulinemia, and coagulability. Increased RI could be considered a marker of systemic atherosclerotic vessel damage, and compounded with reduced eGFR it may significantly increase the cardiovascular and renal risk.

To define subclinical renal damage, previous studies have suggested measurement of albuminuria stage at all of the glomerular filtration rate stages, and the combination of eGFR and albuminuria has been reported to be a useful predictor of cardiovascular disease. Albuminuria is subject to large within-individual variations, with reported coefficient of variation of 50%, and the conclusion as to whether microalbuminuria is present should preferably be based on repeated measurements. On the other hand, RI evaluation is easier because the same probe is used for the heart, and it causes little physical stress to patients. In the context of long-standing hypertension, microalbuminuria and reduction of kidney size might signal the development of nephrosclerosis, which is usually associated with reduced renal blood flow and increased RI. Previous studies found an independent association between RI and albuminuria, and, thus, evaluation of both eGFR and RI instead of albuminuria could be another investigative option to identify essential hypertensive subjects without clinical evidence of cardiovascular disease who are predisposed to worse outcomes. However, further investigation is required to examine these hypotheses.

Previous reports have shown that antihypertensive agents affect RI. Because our study population included patients with treated essential hypertension at the start of the study, our results suggest the importance of evaluating RI to assess cardiovascular and renal outcomes, even in patients receiving antihypertensive medication. These results could, however, underestimate the involvement of BP or RI itself in the development of abnormal renal hemodynamics and cardiovascular events. Other limitations were the relatively short follow-up period and the lack of control over occasional changes in the antihypertensive regimens over time. Even in elderly subjects without renal insufficiency, normal RI can exceed 0.70, and, thus, it remains unclear whether our results apply to very elderly subjects. The relatively small number of events recorded in the present study may have limited the statistical power of our findings.

**Perspectives**

Our findings suggest that impaired renal hemodynamics evaluated by increased RI on the baseline Doppler ultrasound is associated with an increased risk of cardiovascular and renal outcomes and highlight that the combination of high RI and low eGFR may be a powerful predictor of worse outcome in essential hypertension. Especially in hypertensive patients with chronic kidney disease, RI evaluation will complement screening for cardiovascular risk. A large, prospective population-based study will be important to confirm our preliminary observations.

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**Disclosures**

None.

**References**


**Novelty and Significance**

**What Is New?**

- Impaired renal hemodynamics evaluated by increased renal RI on baseline Doppler ultrasonography is associated with an increased risk of cardiovascular and renal outcomes and highlights that the combination of high RI and low eGFR may be a powerful predictor of worse outcome in essential hypertension.

**What Is Relevant?**

- The impact of RI on cardiovascular and renal risk is marked, and identifying renal hemodynamic abnormalities is useful for predicting cardiovascular and renal outcomes, especially in hypertensive patients with chronic kidney disease.

**Summary**

In hypertensive patients with chronic kidney disease, RI evaluation may complement predictors of cardiovascular and renal outcomes.
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Renal Resistive Index and Cardiovascular and Renal Outcomes in Essential Hypertension

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Methods Supplement

Baseline clinical characteristics
Urine albumin concentration was measured by an immunoturbidimetric method. Urine collection was repeated if the patient was menstruating, because this makes albumin measurement unreliable.

Renal ultrasonography and Doppler studies
Ultrasoundographic examinations were performed using duplex Doppler sonography with a Sienna Sonoline ultrasound machine (Siemens, Erlangen, Germany) or Aplio MX ultrasound machine (Toshiba, Tochigi, Japan) with 2.5-MHz pulsed Doppler frequency and 3.5-MHz convex array transducer. The ultrasonographic procedure that we adopted has been described previously. In brief, with the patient in the supine position, pulse rate was calculated from beat-by-beat measurements of Doppler waveforms. The maximum length of the kidneys was determined by B-mode measurements, and intrarenal Doppler signals were obtained from three representative proximal segmental arteries (the first vessels branching off the main renal artery). The Doppler angle chosen was less than 50°, and special care was taken not to compress the kidney and not to have the patient perform a Valsalva maneuver, because both can increase renal RI.

Cardiovascular and Renal Outcomes
The primary endpoint of this study was first occurrence of composite of cardiovascular and renal events including all-cause death, myocardial infarction confirmed by electrocardiographic changes, coronary angiography or myocardial scintigraphy findings, stroke confirmed by clinical symptoms, computed tomography and magnetic resonance angiography or cerebrovascular angiography findings, congestive heart failure requiring hospitalization, aortic dissection, and end stage renal failure requiring regular hemodialysis. Congestive heart failure was defined by the Framingham Heart Study criteria, which require the simultaneous presence of at least two major criteria, or one major criterion in conjunction with two minor criteria, and requiring treatment with diuretics, vasodilators, or antihypertensive drugs. Aortic dissection was defined as any nontraumatic dissection when a participant was admitted to hospital with a dissection that required intervention, and diagnosis was based on confirmatory imaging or intraoperative visualization.
References


