Supplementary Online Content


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eAppendix 1. Study Protocol and Search Strategies

Study protocol for systematic review and meta-analysis to assess the effects of intensive blood pressure control on kidney disease progression in nondiabetic patients with chronic kidney disease

Objective
To synthesize the results of all available randomized clinical trials that compare the effects of treatment with an intensive versus a standard blood pressure target on kidney disease outcome in nondiabetic patients with chronic kidney disease (CKD).

Inclusion Criteria
Study type
- Randomized, parallel-group design clinical trials but not cross-over or cohort design.
- Studies that compared two treatment arms, an intensive blood pressure target versus a standard blood pressure target, to assess kidney disease outcomes.
- Studies that used any class of blood pressure lowering drugs.

Participants
- Eligible studies should have included nondiabetic adult participants older than 18 years.
- Studies with any stage of CKD, except the dialysis population, will be included
- Studies reporting outcomes from nondiabetic CKD subgroups will also be included.

Outcome measures
- Eligible studies should have reported at least one of the following outcomes: annual rate of change in glomerular filtration rate (GFR) (milliliters per minutes per 1.73 m$^2$ per year), doubling of serum creatinine level, or 50% reduction in GFR, end-stage renal disease (ESRD), or all-cause mortality.
- We will also analyze the composite renal outcome of the doubling of serum creatinine level, 50% reduction in GFR, or ESRD.
- We will only analyzed outcomes reported during the in-trial follow-up period.
- ESRD is defined as the need for dialysis therapy or kidney transplantation.

Publication type
- Full-length articles in peer-reviewed journals will be eligible.
- Language of publication will not be restricted.

Data extraction and quality assessment
Two investigators (Wan-Chuan Tsai, Hon-Yen Wu) will independently extract the following information: details of study design, location and published year of study, patients’ characteristics (age, sex, ethnicity, cause of CKD, level of proteinuria), baseline renal function, baseline blood pressure level, target and achieved level of blood pressure in each treatment arm, classes of blood pressure lowering drugs, follow-up duration, outcome events, and adverse events. The methodological quality of eligible trials will be evaluated independently by two investigators (Wan-Chuan Tsai, Hon-Yen Wu) using “the Cochrane Collaboration’s tool for assessing risk of bias” (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias). When relevant information regarding design or outcomes is unclear, or when doubt exists about duplicate publications, the original authors will be contacted for clarifications. Disagreements between the two authors will be resolved by discussion. If the disagreement persists, two other senior investigators (Kuan-Yu Hung, Kuo-Liong Chien) will be consulted to reach a consensus.
**Data Synthesis and Analysis**

All data from each eligible study will be extracted and entered into a spreadsheet (Excel 2007; Microsoft Corporation, Redmond, WA). Categorical variables will be presented as frequencies or percentages, while continuous variables will be presented as mean values, unless stated otherwise. The effect measures from studies with the same outcome will be pooled by meta-analysis. The pooled estimates of effect measures and 95% confidence intervals (CIs) of comparisons between the intensive and standard blood pressure lowering treatments will be calculated using both the fixed-effect model and the DerSimonian and Laird random-effects model. The effect size of continuous outcome (annual rate of change in GFR; mL/min/1.73 m$^2$/y) will be expressed as mean difference (MD) with 95% CI. The annual rate of decline in GFR is significantly slower for the intensive blood pressure lowering treatment if the effect size is significantly greater than zero, and vice versa. Effect sizes of binary outcomes (doubling of serum creatinine or 50% reduction in GFR, ESRD, composite renal outcome, and all-cause mortality) will be expressed as risk ratios (RRs) with 95% CIs. The intensive blood pressure lowering treatment shows a lower risk if the effect size is significantly less than 1, and vice versa. To make an appropriate choice between the fixed-effect and random-effects models, the recommendations of Borenstein were followed. Publication bias will be examined using the funnel plot method and the Egger's regression asymmetry test. Heterogeneity of treatment effects across studies will be assessed by I-squared (I²) and the Cochrane Q-test. We will perform meta-regression using mixed-effects model to explore potential sources of heterogeneity and assess the associations between variables and intervention effects. Variables potentially associated with renal outcomes will be served as covariates in the meta-regression, including age, race, baseline GFR, targeted blood pressure, sample size, and method of GFR measurement, etc. The magnitude of such relationship will be quantified using $R^2$, the proportion of variance explained by the model. Subgroup analysis will be performed if a covariate is significant in the meta-regression. To assess the robustness of the pooled estimates, sensitivity analyses will be undertaken by the same statistical methods after omission of data from specific studies (studies with imputed missing data, studies that did not exclude diabetic subjects). We will also carry out sensitivity analyses by enrolling data of post-trial follow-up periods of the included randomized clinical trials. A two-sided $P \leq 0.05$ is considered statistically significant. Statistical analyses will be performed with R software (version 3.2.4, R Foundation for Statistical Computing, Vienna, Austria).
Search Strategies

We will search the following electronic databases:

1. PubMed
2. MEDLINE
3. Embase
4. Cochrane Library

There will be no restriction on language of publication.

We will search additional studies in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews.

1. PubMed:
Search using the NCBI interface from the earliest available date of indexing through March 24, 2016

("kidney failure, chronic"[Mesh] OR "renal insufficiency, chronic"[Mesh] OR “kidney disease” OR “renal disease”) AND ("Blood Pressure"[Mesh] OR "Arterial Pressure"[Mesh] OR "Hypertension"[Mesh]) AND ("Glomerular Filtration Rate"[Mesh] OR "Creatinine"[Mesh]) AND ("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type]) AND ("control" OR “target” OR “intensive” OR “tight” OR “strict” OR “rigorous”)

2. MEDLINE:
Search using the Ovid interface from the earliest available date of indexing through March 24, 2016

1. exp Kidney Failure, Chronic/
2. exp Renal Insufficiency, Chronic/
3. Kidney Diseases/
4. renal disease.mp.
5. 1 or 2 or 3 or 4
6. blood pressure/
7. arterial pressure/
8. hypertension/
9. 6 or 7 or 8
10. Glomerular Filtration Rate/
11. exp Creatinine/
12. 10 or 11
13. randomized controlled trial/
14. Controlled Clinical Trial/
15. 13 or 14
16. Control.mp.
17. Target.mp.
19. Tight.mp.
20. Strict.mp.
21. Rigorous.mp.
22. 16 or 17 or 18 or 19 or 20 or 21
23. 5 and 9 and 12 and 15 and 22

3. Embase:
Search using the Elsevier interface from the earliest available date of indexing through March 24, 2016

'kidney failure, chronic' OR 'renal insufficiency, chronic' OR 'kidney disease' OR 'renal disease' AND ('blood pressure' OR 'arterial pressure' OR 'hypertension') AND ('glomerular filtration rate' OR 'creatinine') AND
('randomized controlled trial' OR 'controlled clinical trial') AND ('control' OR 'target' OR 'intensive' OR 'tight' OR 'strict' OR 'rigorous')

4. Cochrane Library:
Searched using the Wiley interface from the earliest available date of indexing through March 24, 2016

("kidney failure, chronic" OR "renal insufficiency, chronic" OR “kidney disease” OR “renal disease”) AND
("Blood Pressure" OR "Arterial Pressure" OR "Hypertension") AND ("Glomerular Filtration Rate" OR "Creatinine") AND ("Randomized Controlled Trial" OR "Controlled Clinical Trial") AND ("control" OR “target” OR “intensive” OR “tight” OR “strict” OR “rigorous”)
eAppendix 2. Estimations and Imputations for Missing Data

For essential data to pool the outcome of annual rate of change in GFR, we used estimation and imputation methods to reconstruct the missing values as recommended in the Cochrane Handbook.\textsuperscript{1} The formula: [standard deviation (SD) = \(\sqrt{N} \times \text{standard error (SE)}\)] was used to obtain SD from SE, where N = sample size. The formula: [SD = \(\sqrt{N} \times (\text{upper limit of confidence interval} - \text{lower limit of confidence interval}) / 3.92\)] was used to obtain SD from confidence intervals. In the study reported by Klahr in 1994,\textsuperscript{8} we estimated the annual rate of change in GFR and SD in patients with different levels of proteinuria from the figure. To obtain a mean value of annual GFR decline rate for each study arm in the studies reported by Schrier in 2002,\textsuperscript{9} the means of subgroups were combined using the following formula: \(\frac{N_1M_1 + N_2M_2}{N_1 + N_2}\), where N = sample size, M = mean of each subgroup, and we used SD of the entire study group under the assumption that SD of each study arm was the same. In the study reported by Ruggenenti in 2005,\textsuperscript{10} we substituted the mean value from the median value, imputed the SD from the interquartile range (IQR) using the formula: \[\text{IQR} = 1.35 \times \text{SD}\], and multiplied the monthly data by 12 to estimate the annual data. We used between-group \(P\) value to impute the SD for the study reported by Hayashi in 2010.\textsuperscript{11} For the SD of each study arm in the study reported by Schrier in 2014,\textsuperscript{12} we imputed it from confidence interval of the between-group mean difference, under the assumption that SD of each study arm was the same.
References. References for eAppendix 1 and eAppendix 2


eFigure 1. Summary of Study Identification and Selection

Database search:
144 PubMed
100 MEDLINE
486 Embase
427 Cochrane Library

1 Additional reference identified from hand searching

1158 Retrieved → 328 Duplicates

830 Titles reviewed

677 Excluded due to
- 168 Diabetic subjects
- 150 Not using antihypertensives
- 119 Not assessing blood pressure lowering
- 85 Review articles
- 85 Not chronic kidney disease subjects
- 31 No study results reported
- 26 Not randomized clinical trials
- 12 Not adults
- 1 Letter to editor

153 Abstracts reviewed

139 Excluded due to
- 115 assessing blood pressure lowering
- 11 Not randomized clinical trials
- 5 Review articles
- 4 Diabetic subjects
- 2 Not chronic kidney disease subjects
- 1 Animal study
- 1 Not assessing outcomes of interest

14 Full-text articles reviewed

4 Excluded due to
- 2 Cohort studies
- 2 Not assessing outcomes of interest

10 Articles from 9 randomized clinical trials were included
- 8 reported change in glomerular filtration rate
- 3 reported doubling of serum creatinine or 50% reduction in glomerular filtration rate
- 7 reported end-stage renal disease
- 4 reported composite renal outcome
- 8 reported all-cause mortality
eFigure 2. Summary for Risk of Bias of Included Studies.
The green symbols represent low risk of bias, the yellow symbols represent unclear risk of bias, and the red symbols represent high risk of bias. The figure was generated using Review Manager Version 5.1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashi et al. 2010</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Klahr et al. (Study A), 1994</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Klahr et al. (Study B), 1994</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ruggenenti et al. 2005</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Schrier et al. 2002</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Schrier et al. 2014</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Toto et al. 1995</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wright et al. 2002</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wright et al. 2015</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
eFigure 3. Risk of Bias Graph of Included Studies.
Each methodological quality item is presented as percentages across all included studies. The figure was generated using Review Manager Version 5.1.
eFigure 4. Funnel Plots, Contour-enhanced Funnel Plots, and Egger Regression Asymmetry Test for Assessment of Publication Bias.

(A) Annual rate of change in glomerular filtration rate, (B) Doubling of serum creatinine or 50% reduction in glomerular filtration rate, (C) End-stage renal disease, (D) Composite renal outcome, and (E) All-cause mortality, for comparisons between intensive blood pressure lowering treatments and standard blood pressure lowering treatments. For contour-enhanced funnel plots, contours in black are regions of studies with $P$ values between 0.1–0.05, those in dark gray are $P$ values between 0.05-0.01, and those in gray are $P$ values < 0.01. If studies appear to be missing in areas of high statistical significance, then publication bias is a less likely cause of the funnel asymmetry, and vice versa.
eFigure 5. Sensitivity Analysis Assessing Effects of Intensive Blood Pressure Control on the Annual Rate of Change in Glomerular Filtration Rate by Omitting Studies with Imputed Missing Data.

The unit for the annual rate of change in glomerular filtration rate is mL/min/1.73 m$^2$/y. The pooled effect size are expressed as mean difference (MD) with 95% confidence interval (CI). The annual rate of decline in glomerular filtration rate was significantly slower for intensive control group if MD was significantly greater than zero, and vice versa. SD, standard deviation; and W, weight.
eFigure 6. Sensitivity Analysis Assessing Effects of Intensive Blood Pressure Control on End-stage Renal Disease by Including the Post-trial Follow-up Data of Randomized Clinical Trials.

The post-trial follow-up data of the Modification of Diet in Renal Disease study (Ku et al, 2015) and the African-American Study of Kidney Disease and Hypertension study (Appel et al, 2010) are included. The Modification of Diet in Renal Disease study reported information from Study A and Study B altogether. The intensive control group showed a lower risk if the effect size was significantly less than 1, and vice versa. CI, confidence interval; RR, risk ratio; and W, weight.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensive Events Total</th>
<th>Standard Events Total</th>
<th>Risk Ratio RR</th>
<th>95%-CI W(fixed) W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolto et al, 1995</td>
<td>7 42</td>
<td>2 35</td>
<td>2.92 [0.65; 13.15]</td>
<td>0.5% 0.2%</td>
</tr>
<tr>
<td>Schrier et al, 2002</td>
<td>5 41</td>
<td>3 34</td>
<td>1.38 [0.36; 5.37]</td>
<td>0.7% 0.3%</td>
</tr>
<tr>
<td>Ruggenenti et al, 2005</td>
<td>38 169</td>
<td>34 169</td>
<td>1.12 [0.74; 1.69]</td>
<td>7.7% 3.4%</td>
</tr>
<tr>
<td>Appel et al, 2010</td>
<td>48 540</td>
<td>62 554</td>
<td>0.79 [0.66; 1.14]</td>
<td>13.9% 4.4%</td>
</tr>
<tr>
<td>Ku et al, 2015</td>
<td>308 432</td>
<td>319 408</td>
<td>0.91 [0.84; 0.99]</td>
<td>74.8% 91.1%</td>
</tr>
<tr>
<td>Wright et al, 2015</td>
<td>6 1330</td>
<td>10 1316</td>
<td>0.59 [0.22; 1.63]</td>
<td>2.3% 0.6%</td>
</tr>
<tr>
<td><strong>Fixed effect model</strong></td>
<td><strong>2554</strong></td>
<td><strong>2516</strong></td>
<td><strong>0.92 [0.84; 1.00]</strong></td>
<td>100% --</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>0.91 [0.85; 0.99]</strong></td>
<td><strong>--</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2$-squared=0%; $tau^2$-squared=0; $p=0.4326$
eFigure 7. Forest Plots of Subgroup Analysis Assessing Effects of Intensive Blood Pressure Control on the Annual Rate of Change in Glomerular Filtration Rate, by Different Race Subgroups.

The unit for the annual rate of change in glomerular filtration rate is mL/min/1.73 m$^2$/y. The pooled effect size are expressed as mean difference (MD) with 95% confidence interval (CI). The annual rate of decline in glomerular filtration rate was significantly slower for intensive control group if MD was significantly greater than zero, and vice versa. $P$ for interaction between subgroups = .09. SD, standard deviation; and W, weight.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensive</th>
<th>Standard</th>
<th>Mean difference</th>
<th>MD</th>
<th>95%-CI W(fixed) W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race = Black</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ito et al., 1995</td>
<td>42</td>
<td>35</td>
<td>-0.26</td>
<td>-0.26</td>
<td>[-0.18; 0.10]</td>
</tr>
<tr>
<td>Wright et al., 2002</td>
<td>540</td>
<td>554</td>
<td>-0.26</td>
<td>-0.26</td>
<td>[-0.73; 0.21]</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>682</td>
<td>589</td>
<td></td>
<td>-0.26</td>
<td>[-0.70; 0.10]</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td>-0.26</td>
<td>[-0.70; 0.18]</td>
</tr>
<tr>
<td><strong>Race = Non-Black</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klahr et al. (Study A), 1994</td>
<td>300</td>
<td>285</td>
<td>0.53</td>
<td>0.53</td>
<td>[0.26; 0.82]</td>
</tr>
<tr>
<td>Klahr et al. (Study B), 1994</td>
<td>300</td>
<td>285</td>
<td>0.50</td>
<td>0.50</td>
<td>[0.39; 0.61]</td>
</tr>
<tr>
<td>Schrier et al., 2002</td>
<td>41</td>
<td>34</td>
<td>0.76</td>
<td>0.76</td>
<td>[-1.15; 2.67]</td>
</tr>
<tr>
<td>Ruggenenti et al., 2005</td>
<td>93</td>
<td>80</td>
<td>0.24</td>
<td>0.24</td>
<td>[-1.17; 1.65]</td>
</tr>
<tr>
<td>Hayashi et al., 2010</td>
<td>1230</td>
<td>1269</td>
<td>0.05</td>
<td>0.05</td>
<td>[-0.38; 0.48]</td>
</tr>
<tr>
<td>Schrier et al., 2014</td>
<td>274</td>
<td>284</td>
<td>0.10</td>
<td>0.10</td>
<td>[-0.35; 0.55]</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>2070</td>
<td>2075</td>
<td>0.18</td>
<td>0.18</td>
<td>[-0.08; 0.44]</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td>0.18</td>
<td>[-0.08; 0.46]</td>
</tr>
</tbody>
</table>

| **Fixed effect model**    | 2652      | 2664     | 0.07            | 0.07  | [0.16; 0.29]       | 100% | --                       |
| Random effects model      |           |          |                 | 0.07  | [0.16; 0.29]       | 100% | --                       |

Favoured standard Favoured intensive
eTable 1. Sensitivity Analysis Assessing Effects of Intensive Blood Pressure Control after Omitting Studies Which Did Not Exclude Diabetic Subjects.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N</th>
<th>Fixed-effect Model</th>
<th>Random-effects Model</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effect Size*</td>
<td>95% CI</td>
<td>Effect Size*</td>
</tr>
<tr>
<td>Annual rate of change in GFR</td>
<td>5</td>
<td>-0.05</td>
<td>-0.35 to -0.26</td>
<td>-0.05</td>
</tr>
<tr>
<td>ESRD</td>
<td>5</td>
<td>1.03</td>
<td>0.78 to 1.34</td>
<td>1.03</td>
</tr>
<tr>
<td>Composite renal outcome</td>
<td>3</td>
<td>1.00</td>
<td>0.82 to 1.23</td>
<td>1.00</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6</td>
<td>0.77</td>
<td>0.61 to 0.98</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Note. The effect size for the annual rate of change in GFR (mL/min/1.73 m$^2$/year) is mean difference and those for the remaining outcomes are risk ratio.

Abbreviations. CI, confidence interval; ESRD, end-stage renal disease; GFR, glomerular filtration rate; N, number of studies.
**Table 2. Effects of Intensive Blood Pressure Control on the Annual Rate of Change in Glomerular Filtration Rate among Patients with Different Levels of Proteinuria.**

<table>
<thead>
<tr>
<th>Level of Proteinuria</th>
<th>Characteristics of Studies</th>
<th>Random-effects Model</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, Year</td>
<td>Proteinuria per Day</td>
<td>MD</td>
</tr>
<tr>
<td>&lt; 1 g/day</td>
<td>Klahr et al. (Study A), 1994</td>
<td>Urine protein &lt; 1 g</td>
<td>-0.11</td>
</tr>
<tr>
<td></td>
<td>Klahr et al. (Study B), 1994</td>
<td>Urine protein &lt; 1 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toto et al, 1995</td>
<td>Mean urinary protein: 0.36 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wright et al, 2002</td>
<td>Median UPCR: 0.08 g/g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schrier et al, 2014</td>
<td>Median urinary albumin: 0.02 g</td>
<td></td>
</tr>
<tr>
<td>≥ 1 g/day</td>
<td>Klahr et al. (Study A), 1994</td>
<td>Urine protein &gt; 1 g</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Klahr et al. (Study B), 1994</td>
<td>Urine protein &gt; 1 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ruggenenti et al, 2005</td>
<td>Urine protein &gt; 1 g</td>
<td></td>
</tr>
</tbody>
</table>

Note. The annual rate of change in glomerular filtration rate is expressed in mL/min/1.73 m$^2$/year. All studies estimated urinary protein excretion from 24-hour urine collection. The annual rate of decline in glomerular filtration rate was significantly slower for intensive control group if MD was significantly greater than zero, and vice versa. 

$P$ for interaction between subgroups = .15.

Abbreviations. CI, confidence interval; MD, mean difference; UPCR, urine protein to creatinine ratio.
**Table 3. Effects of Intensive Blood Pressure Control on End-stage Renal Disease among Patients with Different Levels of Proteinuria.**

<table>
<thead>
<tr>
<th>Level of Proteinuria</th>
<th>Characteristics of Studies</th>
<th>Random-effects Model</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, Year</td>
<td>Proteinuria per Day</td>
<td>RR</td>
</tr>
<tr>
<td>&lt; 0.5 g/day</td>
<td>Klahr et al, 1994</td>
<td>Median urinary protein: 0.35 g</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>Toto et al, 1995</td>
<td>Mean urinary protein: 0.36 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wright et al, 2002*</td>
<td>Median UPCR: 0.04 g/g</td>
<td></td>
</tr>
<tr>
<td>≥ 0.5 g/day</td>
<td>Wright et al, 2002*</td>
<td>Median UPCR: 0.66 g/g</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Ruggenenti et al, 2005</td>
<td>Mean urinary protein: 2.9 g</td>
<td></td>
</tr>
</tbody>
</table>

Note. All studies estimated urinary protein excretion from 24-hour urine collection. The intensive control group showed a lower risk if the effect size was significantly less than 1, and vice versa. \( P \) for interaction between subgroups = .43.

*The study of "Wright et al, 2002" defined renal outcomes as either doubling of serum creatinine or end-stage renal disease.

Abbreviations. CI, confidence interval; RR, risk ratio; UPCR, urine protein to creatinine ratio