Effect of Angiotensin-Converting Enzyme Inhibition on Survival in 3773 Chinese Type 2 Diabetic Patients

Wing Yee So, Risa Ozaki, Norman N. Chan, Peter C.Y. Tong, Chung Shun Ho, Christopher W.K. Lam, Gary T.C. Ko, Chun Chung Chow, Wing Bun Chan, Ronald C.W. Ma, Juliana C.N. Chan

Abstract—We assessed the effects of angiotensin-converting enzyme (ACE) inhibition on survival and cardiorenal outcomes in a consecutive cohort of Chinese type 2 diabetic patients with varying degree of albuminuria, ranging from normoalbuminuria to macroalbuminuria. A total of 3773 consecutive Chinese type 2 diabetic patients were followed prospectively for a mean period of 35.8 months. Clinical end points included all-cause mortality, with cardiovascular end point defined as first hospitalization because of ischemic heart disease, congestive heart failure, revascularization procedures, or cerebrovascular accident as well as renal end point defined as dialysis, doubling of baseline plasma creatinine, or plasma creatinine ≥500 μmol/L. The use of ACE inhibitor was 26.3% in normoalbuminuric (NA), 70.1% in microalbuminuric (MI), and 82.6% in macroalbuminuric (MA) groups. Albuminuria was a major predictor for all-cause mortality with 4-fold difference between NA and MA patients. The 7-year cumulative mortality rate was 7.1%, 10.8%, and 21.7% in the NA, MI, and MA groups, respectively. The use of ACE inhibition was associated with significant reduction of mortality (hazard ratio 0.41 and 95% confidence interval, 0.29, 0.58) in the entire group and was most evident in high-risk patients who had cardiorenal complications or retinopathy at baseline for all albuminuric groups (NA 0.76 [0.31,1.87]; MI 0.32 [0.16, 0.65]; and MA 0.20 [0.13, 0.33]). The prognostic value of albuminuria for death in type 2 diabetes and the beneficial effects of ACE inhibitors in Chinese type 2 diabetic patients with micro- or macroalbuminuria has been confirmed. The effects of ACE inhibitors in type 2 diabetic patients with normoalbuminuria require further evaluation. (Hypertension. 2004;44:294-299.)

Key Words: angiotensin-converting enzyme ■ diabetes mellitus ■ cardiovascular diseases ■ renal disease

Type 2 diabetes mellitus is the most common cause of end-stage renal disease, accounting for 40% of all new cases of end-stage renal disease in most developed countries.1,2 Albuminuria is a powerful and independent predictor for death and cardiorenal outcomes in type 2 diabetic patients.3–5 Several landmark studies have confirmed the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors on cardiovascular mortality and morbidity in high-risk patients6 as well as that of angiotensin II (Ang II) antagonists on renal end points in type 2 diabetic patients with left ventricular hypertrophy, clinical proteinuria, and renal insufficiency.7–9 However, the beneficial effect of renin-angiotensin-aldosterone blockade in type 2 diabetic patients with normoalbuminuria is unknown.6,10–12 In this large-scale observational study of Chinese type 2 diabetic patients, we examined the effects of renin-angiotensin-aldosterone system (RAAS) inhibition on survival and cardiorenal outcomes in a consecutive cohort referred to our clinic since 1995 to address these 2 important therapeutic issues.

Methods

Patients and Methods

Between 1995 and 2000, a consecutive cohort of 5004 Chinese type 2 diabetic patients from the Prince of Wales Hospital underwent detailed assessment using the European DiabCare protocol.13 Of these, 3773 who had been observed at least 6 months were included in the analysis. Patients with type 1 diabetes, defined as those presenting with diabetic ketoacidosis, acute presentation with heavy ketonuria (>3.0 mmol/L), or continuous requirement of insulin within 1 year of diagnosis,14 were excluded. Among these 3773 patients, 1419 (37.6%) were considered to be high risk, defined as those with a known history of cardiovascular complications including ischemic heart disease, heart failure, stroke and/or peripheral vascular disease, or renal impairment with plasma creatinine ≥150 μmol/L, or presence of retinopathy at baseline assessment. Low-risk subjects were defined as those without the above complications. The type of ACE inhibitors used included captopril, enalapril, lisinopril, ramipril, and perindopril, whereas losartan, candesartan, and valsartan were the Ang II antagonists used.

Fasting blood samples were taken for measurement of plasma glucose, glycohemoglobin (HbA1c), lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglycerides, and
TABLE 1. Clinical and Biochemical Characteristics of 3773 Type 2 Diabetic Patients Treated With or Without a RAAS Inhibitor

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole Group (n=3773)</th>
<th>Without RAAS Inhibition (n=1944)</th>
<th>With RAAS Inhibition (n=1829)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>59.9±13.4</td>
<td>57.3±13.7</td>
<td>62.7±12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>42.4</td>
<td>41.9</td>
<td>43.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration of diabetes, year</td>
<td>7.5±6.6</td>
<td>6.1±5.9</td>
<td>9.0±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>40.3</td>
<td>41.8</td>
<td>38.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking, current/ever vs npposmoker</td>
<td>28.3</td>
<td>26.7</td>
<td>30.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>137±22</td>
<td>130±20</td>
<td>144±22</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78±11</td>
<td>76±11</td>
<td>79±12</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>97±13</td>
<td>94±12</td>
<td>101±13</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.89±0.07</td>
<td>0.87±0.07</td>
<td>0.90±0.06</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.0±4.0</td>
<td>24.6±3.9</td>
<td>25.5±4.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>7.9±1.9</td>
<td>7.7±1.9</td>
<td>8.1±1.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>9.0±3.5</td>
<td>8.8±3.5</td>
<td>9.3±3.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.4±1.2</td>
<td>5.3±1.2</td>
<td>5.6±1.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total triglyceride, mmol/L</td>
<td>1.4 (0.9,2.1)</td>
<td>1.2 (0.9,1.9)</td>
<td>1.5 (1.1,2.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>1.2±0.4</td>
<td>1.3±0.4</td>
<td>1.2±0.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Plasma creatinine, μmol/L</td>
<td>75 (62.93)</td>
<td>70 (59.85)</td>
<td>82 (66.104)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>4-h albumin excretion rate, μg/min</td>
<td>22.5 (9.1,118.4)</td>
<td>11.3 (7.1,24.2)</td>
<td>81.5 (21.9,937.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Spot urine albumin:creatinine ratio, mg/mmol</td>
<td>2.29 (0.83,12.88)</td>
<td>1.2 (0.6,2.7)</td>
<td>8.4 (1.9,45.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Renal insufficiency, %†</td>
<td>6.8</td>
<td>4.2</td>
<td>9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albuminuric status, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normalalbuminuric</td>
<td>54.9</td>
<td>78.1</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuric</td>
<td>28.1</td>
<td>16.2</td>
<td>40.8</td>
<td></td>
</tr>
<tr>
<td>Macroalbuminuric</td>
<td>17.0</td>
<td>5.7</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td>Presence of cardiovascular complication, %‡</td>
<td>15.2</td>
<td>8.5</td>
<td>22.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of retinopathy, %</td>
<td>36.2</td>
<td>24.8</td>
<td>48.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Causes of death, n, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>45 (26.3)</td>
<td>13 (14.4)</td>
<td>32 (41.0)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>23 (13.1)</td>
<td>16 (16.5)</td>
<td>7 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>107 (61.1)</td>
<td>49 (62.8)</td>
<td>58 (59.8)</td>
<td></td>
</tr>
</tbody>
</table>

mean±SD or median (interquartile range)

*P value is adjusted for age and duration of diabetes.
†Renal insufficiency defined as plasma creatinine ≥150 μmol/L.
‡Cardiovascular complications defined as presence of congestive heart failure, ischemic heart disease, revascularization, cerebrovascular accident, or peripheral vascular disease at baseline.

In this analysis, mortality data were obtained from the Hong Kong Death Registry certified by review of case notes. Details of all medical admissions with primary and secondary diagnosis as well as medication history and last available plasma creatinine results were retrieved from the Central Computerized System at the Hospital Authority Head Office, which is the governing body of all the public hospitals in Hong Kong and captures more than 90% of these data. Cardiovascular end point was defined as hospitalizations because of ischemic heart disease, congestive heart failure, stroke, and revascularization procedures. Renal end point was defined as dialysis or doubling of baseline plasma creatinine or absolute value ≥500 μmol/L.

Laboratory Assays

Plasma glucose was measured by a hexokinase method (Hitachi 911 automated analyzer, Boehringer Mannheim). HbA₁c was measured by an automated ion-exchange chromatographic method (Bio-Rad Laboratory; with reference range 5.1 to 6.4%). Interassay and intraassay coefficients of variation for HbA₁c were ≤3.1% at values <6.5%. Total cholesterol, triglycerides, and HDL-C were measured by enzymatic methods on a Hitachi 911 automated analyzer (Boehringer Mannheim) using reagent kits supplied by the manufacturer of the analyzer. Low-density lipoprotein cholesterol was calculated by the Friedewald equation for TG <4.5 mmol/L. The precision performance of these assays was within the manufacturer’s specifications. Urinary creatinine (Jaffé kinetic method) and albumin (immunoturbidimetry method) were also measured by the Hitachi
A total of 3773 patients with at least 6 months of observational follow-up after assessment between January 1995 and May 2001, with a mean follow-up period of 35.8±18.3 months, were enrolled for survival analysis. At baseline, 2048 (54.9%) patients had normoalbuminuria (NA), 1047 (28.1%) had microalbuminuria (MI), and 634 (17.0%) had macroalbuminuria (MA). The use of RAAS inhibitors was 26.3%, 70.1%, and 82.6% in NA, MI, and MA patients, respectively.

The majority of these patients (84.3%) were treated with an ACE inhibitor (Table 1). A small proportion (15.7%) of patients had been treated with an ACE inhibitor and then switched to an Ang II antagonist or treated with an Ang II antagonist alone. For patients in whom the RAAS inhibition was discontinued (n=144), the reasons for discontinuation as recorded in the case notes were as follow: 12.0% because of cough, 6.3% because of hyperkalaemia, and 18.4% because of increased plasma creatinine. In 38.6% of patients, the reasons for treatment discontinuation were unclear.

Figures 1 and 2 and Table 2 show the cumulative mortality in patients categorized according to their baseline albuminuric status and the effects of RAAS inhibition on all-cause mortality. Tables 3 and 4 show the major determinants of mortality in the patient group, which included increased age, male sex, albuminuric status, cardiovascular complications at baseline, and nonusage of RAAS inhibition.

Albuminuria was an independent predictor for all-cause mortality with a 4-fold difference between NA and MA patients (HR 4.75 [95% CI, 3.35, 6.72; \( P<0.001 \)) and 2-fold difference between NA and MI patients (HR1.86 [95% CI, 1.27, 2.72; \( P=0.001 \)). The 7-year cumulative mortality rate was 7.1%, 10.8%, and 21.7% in NA, MI, and MA groups, respectively. Using Cox regression analysis, for every 1 natural log-value increase in albumin excretion rate, the HR for death was increased by 1.39 (95% CI, 1.30, 1.49; \( P<0.001 \); Figure 1 and Tables 3 and 4).

The use of RAAS inhibitors significantly reduced mortality even after controlling for other confounding factors (HR 0.41 [95% CI, 0.29, 0.58]; Tables 2, 3, and 4). On subgroup analysis, RAAS inhibition had a neutral effect in the NA group but showed distinct benefits in the MI and, especially, MA groups (Figure 2, Table 2), particularly for those with cardiovascular complications, renal insufficiency, or retinop-
TABLE 3. Univariate Analysis Using Cox Regression Model for Hazard Ratios (95% Confidence Interval) of Various Predictors for All-Cause Mortality in 3773 Type 2 Diabetic Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.08 (1.07,1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>1.06 (1.04,1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, current/ex-smoker</td>
<td>2.13 (1.58,2.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.62 (1.20,2.18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>1.02 (0.01,1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>1.00 (0.98,1.01)</td>
<td>0.53</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>5.07 (1.15,22.24)</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.93 (0.89,0.97)</td>
<td>0.0006</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>0.95 (0.87,1.03)</td>
<td>0.18</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>0.99 (0.88,1.12)</td>
<td>0.90</td>
</tr>
<tr>
<td>Ln total triglyceride, mmol/L</td>
<td>1.00 (0.79,1.27)</td>
<td>0.99</td>
</tr>
<tr>
<td>Ln 4-hour albumin excretion rate, μg/min</td>
<td>1.39 (1.30,1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of macrovascular complications</td>
<td>4.06 (2.96,5.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of retinopathy, %</td>
<td>3.31 (2.42,4.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Usage of RAAS inhibition</td>
<td>1.15 (0.85,1.56)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Time-to-event analyses using Cox regression to calculate the risk of mortality. Risk was expressed in hazard ratio with 95% confidence interval.

TABLE 4. Multivariate Analysis Using Cox Regression Model for Hazard Ratios (95% Confidence Interval) of Various Predictors for All-Cause Mortality in 3773 Type 2 Diabetic Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.07 (1.05,1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.58 (1.14,2.18)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ln 4-hour albumin excretion rate, μg/min</td>
<td>1.42 (1.31,1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of macrovascular complications</td>
<td>2.05 (1.45,2.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Usage of RAAS inhibition</td>
<td>0.42 (0.30,0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAAS inhibition throughout study period*</td>
<td>0.03 (0.004,0.22)</td>
<td>0.0006</td>
</tr>
<tr>
<td>RAAS inhibition subsequently*</td>
<td>0.02 (0.004,0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAAS inhibition terminated*</td>
<td>2.02 (1.42,2.87)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Time-to-event analyses using Cox regression to calculate the risk of mortality. Risk was expressed in hazard ratio with 95% CI.

Other independent variables included smoking status (current/ex-smoker vs nonsmoker), duration of diabetes, systolic blood pressure, presence of retinopathy at baseline, body mass index. Waist-to-hip ratio was not selected in the model, whereas diastolic blood pressure, total cholesterol, total triglyceride, and HbA₁c were not significant in the univariate analysis as shown in Table 3 and were not entered in the model.

*Different pattern of usage of RAAS inhibition compared to patients who were never put on RAAS inhibition.

The effect of different patterns of RAAS inhibitor usage on survival is shown in Figure 3. Patients who were treated with a RAAS inhibitor at baseline that was subsequently discontinued had the highest annualized all-cause mortality rate of 5.0%. This is compared with 1.4% in patients who had never been put on RAAS inhibitors, 1.7% in those who persisted with a RAAS inhibitor from baseline, and 1.2% for those who commenced subsequently and persisted with treatment after baseline assessment (P<0.001). Patients in whom treatment with RAAS inhibitor was discontinued had lower baseline HDL-C (1.2±0.4 versus 1.3±0.4 mmol/L, P=0.04), higher plasma creatinine (101 [78,171] versus 91 [75,117] μmol/L, P<0.001), and higher prevalence of retinopathy (65.6% versus 56.2%, P=0.04) compared with the group having persistent use. All results remained the same when time weighing was taken into account.

Discussion

The results of this large-scale cohort study indicate that inhibition of the RAAS with ACE inhibitors or Ang II antagonists was associated with a significant reduction in
mortality and renal end points in high risk patients with
known diabetic complications or those with clinical protein-
uria or renal insufficiency. No significant outcome benefits
were shown in those with normoalbuminuria within the
modest follow-up period. These results are in accordance
with the greater benefits of Ang II inhibition in patients with
severe proteinuria or renal insufficiency (e.g, plasma creati-
nine ≥200 μmol/L) in the Reduction of Endpoints in Non-
insulin-dependent diabetes mellitus with the Angiotensin II
Antagonist Losartan (RENAAL) and Irbesartan Diabetic
Nephropathy Trial (IDNT) studies.7,8 We found that patients
with RAAS inhibition had more than 50% risk reduction for
all-cause mortality in microalbuminuric patients and 80% in
the macroalbuminuric group compared with their counter-
parts. More importantly, this benefit was highlighted by the
similar death rate between macroalbuminuric patients treated
with a RAAS inhibitor and microalbuminuric patients not
treated with the drug (Figure 2). Translating the results of our
study into the number needed to treat, only 3 macroalbu-
muric patients needed to be treated to prevent 1 case of
death or end-stage renal disease when other risk factors were
optimized.

Although there is a large body of evidence from clinical
trials supporting the cardiorenal protective effects of RAAS
inhibition in type 2 diabetic patients,6–8 their effectiveness in
clinical practice, especially for low-risk patients, remains to
be determined.17 In the United Kingdom Prospective Diabetes
clinical practice, especially for low-risk patients, remains to
the rate of decline in renal function once albuminuria pro-
ceeds.6 In the United Kingdom Prospective Diabetes
Study, treatment with an ACE inhibitor (captopril) had
similar effects on clinical outcomes in hypertensive type 2
diabetic patients compared with treatment with a β-blocker
(atenolol) although the albuminuric status of these patients
was not clearly defined.12 Similarly, the Enalapril Efficacy
in Nephropathy Study also failed to confirm the renoprotective
effect of ACE inhibitors in normotensive type 2 diabetic
patients in the initial period, although ACE inhibitors reduced
the rate of decline in renal function once albuminuria pro-
gressed.11 In our analysis, RAAS inhibition had neutral
effects in patients with normoalbuminuria after adjustment
for baseline cardiovascular and metabolic profile. It is plau-
sible that beneficial effects (if any) conferred by RAAS
inhibition in normoalbuminuric type 2 diabetic subjects may
only become apparent with longer follow-up duration.
Clearly future studies with longer term follow-up would be
required to address this issue.

A remarkable finding of our study is that patients treated
with ACE inhibitors, which were subsequently discontinued,
had the highest annualized mortality compared with those
who had never been treated with RAAS inhibitors. This
reflects the high-risk group, which warranted ACE inhibitors,
and this finding is consistent with those of the MICRO-Heart
Outcomes Prevention Evaluation (HOPE) substudy.6 Our
results also indicate that physicians should consider using
Ang II antagonist as an alternative in high-risk patients who
are unable to tolerate ACE inhibitors.

Interestingly, we found that malignancy was the main
cause of death among patients who were not treated with
RAAS inhibition. The underlying explanation for this obser-
vation is unclear, but our results are consistent with other
previous study findings.18,19 Our study was not designed to
investigate this issue; hence, further studies specifically
designed to address this issue would be required.

Study Limitations
Several potential limitations of this large-scale study warrant
further discussion. First, this study cohort was recruited from
1995 to 2000, a time before publication of several landmark
studies such as RENAAL, IDNT, and the Losartan Interven-
tion For Endpoint reduction in hypertension (LIFE). Hence,
most of the patients were treated with ACE inhibitors rather
than Ang II antagonists (n=321). Nevertheless, the results
were similar after we excluded this latter group of patients.
Second, this study was not randomized, which caused a
degree of selection bias. Third, our study results could be
affected by confounding factors or bias in the analysis
because the analysis did not take into account changes in
antihypertensive therapy. Lastly, reasons for discontinuation
of RAAS inhibition therapy were not clearly documented in
nearly 40% of patients, which might confound the inference
regarding the cause of death or morbidity. Despite the above
limitations, and without any monitoring of drug compliance,
we were able to show very significant beneficial results of
RAAS inhibition in micro- and macroalbuminuric type 2
diabetic patients in this very large-scale cohort of Hong Kong
Chinese, a population in which evidence for the beneficial
effects of long-term RAAS inhibition is lacking.

Perspectives
In this prospective cohort analysis involving 3773 Chinese
type 2 diabetic patients, we have confirmed the prognostic
value of albuminuria in terms of all-cause mortality in this
population. In support of results from major clinical trials, the
beneficial effects of RAAS inhibitors can be translated in
clinical practice, especially in high-risk patients with albu-
muria, renal insufficiency, history of cardiovascular com-
plications, and retinopathy. Discontinuation of these drugs in
high-risk patients was associated with early death compared
with those who continued with treatment. The effects of
RAAS inhibition in low-risk, normoalbuminuric patients with
type 2 diabetes require further evaluation.

Acknowledgments
We are most grateful to Professor H.H. Parving of Steno Diabetes
Centre, Netherland and Dr Benny Zee, director of the Comprehen-
sive Clinical Trial Centre of the Chinese University of Hong Kong
for their critical appraisal. Special thanks are extended to Dr Fung
Hong, deputy director, and Edwina Chu, senior statistician, of the
Hong Kong Hospital Authority Headquarter for their assistance in
retrieving the data on clinical outcomes and Albert Cheung, com-
puter officer, of the Centre for Clinical Trials and Epidemiological
Research for his assistance in data analysis. We thank all medical
and nursing staff at the Prince of Wales Hospital Diabetes Centre

for their commitment and dedication in implementing the structured
diabetes care protocol and its continuous quality improvement. We
are most grateful to Kevin H.M. Yu for computerizing and managing
the Prince of Wales Hospital Diabetes Registry.

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Hypertension. 2004;44:294-299; originally published online July 12, 2004;
doi: 10.1161/01.HYP.0000137192.19577.c3

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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