Effect of Candesartan on Microalbuminuria and Albumin Excretion Rate in Diabetes
Three Randomized Trials

Rudy Bilous, MD; Nish Chaturvedi, MD; Anne Katrin Sjølie, MD; John Fuller, MD; Ronald Klein, MD; Trevor Orchard, MD; Massimo Porta, MD; and Hans-Henrik Parving, MD*

Background: Microalbuminuria in diabetes is strongly predictive of nephropathy, end-stage renal disease, and premature cardiovascular morbidity and mortality. Effective preventive therapies are therefore a clinical priority.

Objective: To determine whether the angiotensin-receptor blocker candesartan compared with placebo affects microalbuminuria incidence or rate of change in albuminuria in type 1 and type 2 diabetes.

Design: 3 randomized trials of the DIRECT (Diabetic Retinopathy Candesartan Trials) Program.

Setting: 309 secondary care centers.

Patients: 3326 and 1905 patients with type 1 and type 2 diabetes, respectively. Most were normotensive, and all had normoalbuminuria (median urinary albumin excretion rate, 5.0 µg/min).

Intervention: Candesartan, 16 mg/d increasing to 32 mg/d, versus placebo. Assignment was done centrally using an interactive voice-response system. Patients, caregivers, and researchers were blinded to treatment assignment. During a median follow-up of 4.7 years, 793 patients discontinued therapy and 63 were lost to follow-up.

Measurements: Urinary albumin excretion rate, assessed annually by 2 overnight collections; if it was 20 µg/min or greater, then 2 further collections were done. The primary end point was new microalbuminuria (3 or 4 collections of urinary albumin excretion rate ≥20 µg/min). The secondary end point was rate of change in albuminuria.

Results: Individual and pooled results of the 3 trials showed that candesartan had little effect on risk for microalbuminuria (pooled hazard ratio, 0.95 [95% CI, 0.78 to 1.16]; P = 0.60). Pooled results showed that the annual rate of change in albuminuria was 5.53% lower (CI, 0.73% to 10.14%; P = 0.024) with candesartan than with placebo.

Limitations: Investigators recruited mainly normotensive patients or patients with well-controlled hypertension who were at low overall vascular risk, which resulted in a low rate of microalbuminuria. Studies were powered for retinal and not renal end points.

Conclusion: Candesartan, 32 mg/d, for 4.7 years did not prevent microalbuminuria in mainly normotensive patients with type 1 or type 2 diabetes.

Primary Funding Source: AstraZeneca and Takeda.


For author affiliations, see end of text.

ClinicalTrials.gov registration numbers: NCT00252733, NCT00252720, and NCT00252694.

* For a list of members and investigators of the DIRECT (Diabetic Retinopathy Candesartan Trials) Program Study Group, see the Appendix (available at www.annals.org).

This article was published at www.annals.org on 19 May 2009.
context
The role of angiotensin-receptor blockers in the primary prevention of microalbuminuria is unclear.

Contribution
These 3 randomized trials assessed whether candesartan prevented microalbuminuria more than placebo in adults with normoalbuminuria. All participants had either type 1 or type 2 diabetes, and most were normotensive. Individual and pooled results of the 3 trials showed similar rates of development of microalbuminuria with candesartan or placebo over a 4- to 5-year follow-up.

Implication
Renin–angiotensin system blockade with an angiotensin-receptor blocker did not prevent microalbuminuria in mostly normotensive people with diabetes.

—The Editors

moalbuminuric patients with type 1 or type 2 diabetes. Retinopathy results have previously been published (8, 9). The incidence of microalbuminuria was a prespecified primary end point in the pooled study population; the rate of change in UAER was a prespecified secondary end point in each study and in the pooled study population. These analyses make up the DIRECT-Renal study. The Appendix (available at www.annals.org) lists members and investigators of the DIRECT Program Study Group.

Methods
Design Overview
The DIRECT protocol and baseline patient characteristics are described elsewhere (8–11). In brief, the research program comprised 3 related studies to investigate the effect of candesartan on 1) incidence of retinopathy (DIRECT-Prevent 1) in 1421 type 1 diabetic patients (age 18 to 50 years; diabetes duration, 1 to 15 years) who were normotensive (mean sitting blood pressure ≤130/85 mm Hg) and normoalbuminuric (UAER <20 μg/min in at least 1 of 2 timed overnight urine collections); 2) progression of mild or moderate retinopathy (DIRECT-Protect 1) in 1905 type 1 diabetic patients (age 18 to 55 years; diabetes duration, 1 to 20 years) who were normotensive and normoalbuminuric; and 3) progression of mild or moderate retinopathy (DIRECT-Protect 2) in 1905 type 2 diabetic patients (age 37 to 75 years; diabetes duration, 1 to 20 years) who were normoalbuminuric and either were normotensive or had controlled hypertension (defined as blood pressure ≤160/90 mm Hg) with non–RAS-blocker therapy.

We excluded patients if they had eye conditions that precluded us from analyzing retinal photographs; clinically significant macular edema, proliferative retinopathy, or stenotic valvular heart disease; recent stroke or myocardial infarction; or a clinical indication for or contraindication to RAS-blocking agents. We also excluded pregnant or lactating women and patients with renal impairment (serum creatinine level ≥110 μmol/L [≥1.2 mg/dL] in women and ≥130 μmol/L [≥1.5 mg/dL] in men). Antihypertensive therapy was permitted only in patients with type 2 diabetes. Other exclusion criteria are listed in the study protocol, which is available at www.clinicaltrials.gov.

Recruitment commenced in August 2001, and the last patient was studied in March 2008. The minimum follow-up was 4 years. The DIRECT Program was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice. The studies were approved by each participating center’s ethics committee, and all participants gave written informed consent.

Setting and Participants
A total of 309 study sites in 30 countries participated. The sites were secondary care facilities with access to retinal photography. Approximately 50% of randomly assigned patients were recruited in Russia and central and eastern Europe, 17% in western Europe, 14% in South Africa, 12% in Israel, 3% in Canada, and 3% in Oceania (including Australia and New Zealand). Investigators for all 3 studies recruited at all sites synchronously. Details of the baseline characteristics of the study participants have been published (11).

Randomization and Interventions
We randomly assigned eligible patients centrally using an interactive voice-response system to either placebo or candesartan, 16 mg/d increasing to 32 mg/d after 1 month. We generated separate randomization schedules for each study. We stratified randomization by hypertensive status in DIRECT-Protect 2 only, but we used no other stratification variable. Investigators, caregivers, and participants were unaware of treatment allocation. Dose adjustment to 16 mg or 8 mg could be made at any time. Full details of the retinal studies are published elsewhere (8, 9).

Patients were seen every 6 months for at least 4 years. Routine serum biochemistry, total and high-density lipoprotein cholesterol, and glycated hemoglobin A1c (HbA1c) (aligned to DCCT standards) were measured in a central laboratory.

We measured UAER in 2 timed overnight collections by using nephelometry (Beckmann Array, Beckmann Instruments, High Wycombe, United Kingdom) at baseline and annually thereafter. The lower limit of detection of albumin concentration was 20 μg/L, with a maximum allowable coefficient of variation of 5% in the mean range of 50 to 100 μg/L.

We asked patients who developed microalbuminuria (UAER ≥20 μg/min) in 1 or both urine samples at any time to provide 2 more samples. If 3 or 4 of these 4 con-
consecutive samples were positive, we considered this to constitute a microalbuminuria event and allowed open-label ACE inhibitor therapy.

We measured blood pressure after the patient sat still for at least 5 minutes by using an automated device (Omron M4, Omron Healthcare Company, Kyoto, Japan) with an appropriate-size cuff. Among 3 readings, the mean of the last 2 was used in the analysis. Patients who were or became hypertensive (blood pressure \( > 140/85 \) mm Hg) but whose UAER remained normal could be prescribed any non–RAS-blocking antihypertensive agent according to international and national clinical guidelines.

**Measurements and Outcomes**

The main a priori–determined end point for the pooled analysis of the 3 trials was development of microalbuminuria. Rate of change in UAER was a predefined secondary end point for each trial, as well as for the pooled analysis. The primary outcome for all trials, results of which have been published (8, 9), was incidence and progression of retinopathy.

**Follow-up Procedures**

A steering committee of senior investigators and representatives of the funding companies oversaw the study. ICON (Dublin, Ireland) did site monitoring to standard

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**Figure 1. Study flow diagram for patients with type 1 diabetes.**

Number of patients who did not complete renal functional assessments includes those who died or were lost to follow-up. DIRECT = Diabetic Retinopathy Candesartan Trial; MA = microalbuminuria.
quality control procedures. ICON staff collected all data centrally and transferred data to the study sponsors. An independent safety committee met regularly and reviewed unblinded data. An independent statistical advisor reviewed and verified all results before publication.

**Statistical Analysis**

Statistical staff at AstraZeneca and Takeda did analyses according to the intention-to-treat principle. The 2-sided P values were calculated without any adjustment for multiple comparisons.

We analyzed the incidence of microalbuminuria by using the time from randomization to first incidence. Because urine was collected at prescheduled times, with microalbuminuria occurring between these collections, we did not know the exact date of the event and consider the data to be interval-censored.

To compare the incidence of renal end points in the placebo and candesartan groups, we used a stratified generalized log-rank test for interval-censored failure time data (12). The P value for this test was calculated together with the estimated time to microalbuminuria for the 2 groups. We also did the analysis for each study separately. We estimated the treatment effect by calculating a 95% CI for the hazard ratio (HR) by using a generalized Cox regression model (13). These analyses were adjusted for the following prespecified baseline characteristics: duration of diabetes, HbA1c, systolic blood pressure, UAER, and treatment of hypertension (DIRECT-Protect 2 only).

We based sample size on retinopathy end points for each study. For DIRECT-Renal, assuming an annual incidence of microalbuminuria of 2% in the placebo group, the log-rank test would have been able to detect a 24% relative risk reduction with a power of 80%.

The analysis of the annual rate of change in UAER used the estimate of the slope of a fitted regression line through the origin for each patient, excluding the baseline UAER. The log-transformed UAER served as the dependent variable and time from randomization in years as the independent variable. We then compared the mean slopes between placebo and candesartan in a linear multiple regression model with treatment, study, and log-transformed UAER as explanatory variables (14).

We calculated summary statistics for key baseline characteristics in patients who did versus those who did not develop microalbuminuria. We used a proportional hazard model, stratified for study only, to identify the variables that affect the progression of microalbuminuria. The following baseline characteristics were included in the model: age, duration of diabetes, HbA1c value, degree of retinopathy, serum non–high-density lipoprotein cholesterol level, systolic blood pressure, diastolic blood pressure, sex, smoking history, and randomized group.

We used SAS, version 8.2 (SAS Institute, Cary, North Carolina), for the analyses and East, version 5.2 (Cytel, Cambridge, Massachusetts), for the sample size calculations.

**Role of the Funding Source**

The DIRECT Program was funded by AstraZeneca and Takeda. The funding sources had no role in the study design, interpretation of the data, or preparation in or decision to submit the manuscript. Employees of the funding companies did the statistical analysis, which was checked by an independent consultant. Representatives of the funding companies were nonvoting members of the steering committee. The authors had complete control over the interpretation of the results and the writing of the manuscript.
RESULTS

Figures 1 and 2 show the numbers of patients who were enrolled and recruited and who completed, withdrew from, or did not complete the study (and reasons why). A total of 793 patients discontinued treatment during the trial and 63 patients were lost to follow-up. At the last visit, 80.6% of patients were receiving the maximum dose of candesartan (32 mg/d).

Table 1 shows baseline data by treatment group in the 3 studies and the pooled study population. Patients with type 1 diabetes were younger and had a lower body mass index than patients with type 2 diabetes. Blood pressure was within the normal range for the type 1 diabetic patients and was well controlled in the 62% of type 2 diabetic patients treated for hypertension. Among the type 2 diabetic patients treated for hypertension, 67% were receiving 1 drug and 27% were receiving 2 drugs. Hemoglobin A1c levels were slightly higher in DIRECT-Prevent 1 and DIRECT-Protect 1 and for patients not receiving antihypertensive medication in DIRECT-Protect 2.

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>DIRECT-Prevent 1</th>
<th>DIRECT-Protect 1</th>
<th>DIRECT-Protect 2</th>
<th>Pooled DIRECT Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>711</td>
<td>710</td>
<td>951</td>
<td>954</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>29.6 (8.0)</td>
<td>29.9 (8.1)</td>
<td>35.1 (8.5)</td>
<td>31.9 (8.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>413 (58)</td>
<td>392 (55)</td>
<td>538 (57)</td>
<td>553 (58)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>690 (97)</td>
<td>685 (97)</td>
<td>928 (98)</td>
<td>943 (99)</td>
</tr>
<tr>
<td>Mean duration of diabetes (SD), y</td>
<td>6.6 (3.9)</td>
<td>6.8 (3.9)</td>
<td>10.9 (4.3)</td>
<td>11.0 (4.3)</td>
</tr>
<tr>
<td>Mean HbA1c, level (SD)*</td>
<td>8.0 (1.7)</td>
<td>8.2 (1.7)</td>
<td>8.5 (1.6)</td>
<td>8.5 (1.6)</td>
</tr>
<tr>
<td>Treated for hypertension, n (%)</td>
<td>2 (0.3)</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>β-Blocker (SD)</td>
<td>0 (0.1)</td>
<td>1 (0.1)</td>
<td>0 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Diuretic (SD)</td>
<td>0</td>
<td>0 (0.1)</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Calcium-channel blocker (SD)</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean SBP (SD), mm Hg†</td>
<td>116 (9.5)</td>
<td>116 (9.6)</td>
<td>117 (9.6)</td>
<td>117 (9.8)</td>
</tr>
<tr>
<td>Mean DBP (SD), mm Hg†</td>
<td>72 (6.9)</td>
<td>72 (7.3)</td>
<td>74 (6.5)</td>
<td>73 (6.5)</td>
</tr>
<tr>
<td>Mean DBP with antihypertensive medication (type 2 diabetes only) (SD), mm Hg</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Smoker, n</td>
<td>490</td>
<td>471</td>
<td>610</td>
<td>630</td>
</tr>
<tr>
<td>Never</td>
<td>490</td>
<td>471</td>
<td>610</td>
<td>630</td>
</tr>
<tr>
<td>Former</td>
<td>50</td>
<td>47</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Current</td>
<td>171</td>
<td>192</td>
<td>260</td>
<td>243</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>23.8 (3.2)</td>
<td>24.1 (3.5)</td>
<td>24.7 (3.7)</td>
<td>24.6 (3.5)</td>
</tr>
<tr>
<td>Mean total cholesterol level (SD)</td>
<td>4.7 (1.0)</td>
<td>4.8 (1.1)</td>
<td>4.8 (0.9)</td>
<td>4.8 (0.9)</td>
</tr>
<tr>
<td>mg/dl</td>
<td>181 (39)</td>
<td>185 (42)</td>
<td>185 (35)</td>
<td>185 (35)</td>
</tr>
<tr>
<td>Mean HDL cholesterol level (SD)</td>
<td>1.7 (0.4)</td>
<td>1.7 (0.4)</td>
<td>1.7 (0.4)</td>
<td>1.7 (0.4)</td>
</tr>
<tr>
<td>mg/dl</td>
<td>66 (15)</td>
<td>66 (15)</td>
<td>66 (15)</td>
<td>66 (15)</td>
</tr>
<tr>
<td>Mean serum creatinine level (SD)</td>
<td>90.5 (13.6)</td>
<td>89.7 (13.6)</td>
<td>90.2 (13.2)</td>
<td>91.3 (13.4)</td>
</tr>
<tr>
<td>μmol/L</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>mg/dl</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.4)</td>
</tr>
<tr>
<td>Mean serum potassium level, (SD)</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.4)</td>
</tr>
<tr>
<td>Median UAER (25th, 75th percentiles), μg/min</td>
<td>4.5 (3.0, 6.5)</td>
<td>4.5 (3.0, 7.0)</td>
<td>5.0 (3.5, 7.0)</td>
<td>5.0 (3.5, 7.5)</td>
</tr>
</tbody>
</table>

BMI = body mass index; DBP = diastolic blood pressure; DIRECT = Diabetic Retinopathy Candesartan Trial; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; SBP = systolic blood pressure; UAER = urinary albumin excretion rate.

† Mean values for all patients in DIRECT-Prevent 1 and DIRECT-Protect 1 and for patients not receiving antihypertensive medication in DIRECT-Protect 2.

Among patients with type 2 diabetes in the candesartan and placebo groups, 36% were receiving insulin, and approximately equal proportions in each group were receiving sulfonylureas (53.8% vs. 56.2%), metformin (22.7% vs. 20.4%), and thiazolidinediones (0.9% vs. 0.9%).

The mean follow-up was 4.7 years for the pooled study population, DIRECT-Prevent 1, and DIRECT-Protect 2 and 4.8 years in DIRECT-Protect 1. For the pooled study population, blood pressure was 3.3/2.3 mm Hg lower in the candesartan group than in the placebo group by the end of the study (P < 0.001). In DIRECT-Prevent 1 and DIRECT-Protect 1, blood pressure was 2.6/2.7 mm Hg and 3.6/2.5 mm Hg lower in the candesartan group, respectively (P < 0.005). Among patients...
who did and did not receive antihypertensive therapy in DIRECT-Protect 2, blood pressure was 2.9/3.1 mm Hg and 4.3/2.5 mm Hg lower, respectively, in the candesartan group (\( P \leq 0.005 \)). These blood pressure differences were apparent by the 3-month follow-up and were sustained throughout the trial.

Among patients in the candesartan and placebo groups, 47 and 31 in DIRECT-Prevent 1, 53 and 50 in DIRECT-Protect 1, and 46 and 53 in DIRECT-Protect 2, respectively, were censored at baseline because they did not complete the necessary number of urine collections for the renal end point (Figures 1 and 2).

Similar numbers of patients in the candesartan and placebo groups developed microalbuminuria in each of the 3 studies (Table 2). For the pooled study population, the unadjusted HR (candesartan vs. placebo) was 0.95 (95% CI, 0.78 to 1.16; \( P = 0.60 \)) (Figure 3), with little change in response to adjustment for key baseline covariates or for systolic blood pressure over the duration of the trial. The HRs for the individual studies did not qualitatively differ from that of the pooled analysis.

Table 3 shows the cumulative percentage of patients who developed microalbuminuria in each study (separating the hypertensive and normotensive patients in DIRECT-Protect 2). The percentage of patients who began open-label RAS-blocker therapy and the median UAER are also included. The number of patients who developed microalbuminuria did not differ between groups for any of the studies, regardless of previous antihypertensive therapy. More patients in the placebo group than in the candesartan group received open-label RAS-blocking agents during the study (396 patients vs. 275 patients; chi-square \( P < 0.001 \)) for various indications. The primary outcome was not affected by adjustment for open-label RAS-blocking agents or by censoring the data at the time of first use (data not shown).

An evaluation of the baseline characteristics of the 401 patients who developed microalbuminuria showed, in a multivariate model, that a 1-\( \mu g/\text{min} \) increase in baseline UAER (HR, 1.020 [CI, 1.016 to 1.023]), an increase in retinopathy by 1 ETDRS (Early Treatment Diabetic Retinopathy Study) level (HR, 1.180 [CI, 1.110 to 1.255]), a 1% increase in HbA1c value (HR, 1.265 [CI, 1.194 to 1.340]), and male sex (HR, 1.531 [CI, 1.233 to 1.901]) were predictive of microalbuminuria (\( P < 0.001 \)).

Median UAER did not differ at any time point in both groups (data not shown). Table 2 shows the candesartan–placebo ratio for annual rate of change in UAER for the 3 studies. A 5.53% reduction (CI, 0.73% to 10.14%; \( P = 0.024 \)) occurred in the pooled study population, which equates to an absolute reduction of 0.11 \( \mu g/\text{min} \).

The frequency of reported adverse events was similar for both groups in all 3 studies (Table 4) and is reported elsewhere (8, 9). Reported hyperkalemia rates during the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Candesartan</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIRECT-Prevent 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of microalbuminuria per 1000 patient-years (95% CI)</td>
<td>6 (3.5–9.2)</td>
<td>5 (3.1–8.7)</td>
<td>1.08 (0.54–2.19)</td>
</tr>
<tr>
<td>Least-squares mean of annual rate of change in UAER (95% CI), ( \mu g/\text{min} )</td>
<td>0.51 (0.49–0.53)</td>
<td>0.54 (0.52–0.57)</td>
<td>0.97 (0.94–1.00)</td>
</tr>
<tr>
<td><strong>DIRECT-Protect 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of microalbuminuria per 1000 patient-years (95% CI)</td>
<td>16 (12.8–20.9)</td>
<td>16 (12.6–20.7)</td>
<td>1.03 (0.72–1.46)</td>
</tr>
<tr>
<td>Least-squares mean of annual rate of change in UAER (95% CI), ( \mu g/\text{min} )</td>
<td>0.57 (0.49–0.65)</td>
<td>0.64 (0.56–0.72)</td>
<td>0.93 (0.83–1.04)</td>
</tr>
<tr>
<td><strong>DIRECT-Protect 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive use at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of microalbuminuria per 1000 patient-years (95% CI)</td>
<td>36 (28.7–44.7)</td>
<td>36 (28.4–44.5)</td>
<td>1.01 (0.74–1.39)</td>
</tr>
<tr>
<td>Least-squares mean of annual rate of change in UAER (95% CI), ( \mu g/\text{min} )</td>
<td>0.68 (0.60–0.76)</td>
<td>0.73 (0.66–0.81)</td>
<td>0.95 (0.85–1.06)</td>
</tr>
<tr>
<td>Normotensive at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of microalbuminuria per 1000 patient-years (95% CI)</td>
<td>29 (21.2–39.4)</td>
<td>40 (30.5–52.6)</td>
<td>0.73 (0.48–1.10)</td>
</tr>
<tr>
<td>Least-squares mean of annual rate of change in UAER (95% CI), ( \mu g/\text{min} )</td>
<td>0.62 (0.57–0.67)</td>
<td>0.69 (0.65–0.74)</td>
<td>0.93 (0.87–0.99)</td>
</tr>
</tbody>
</table>

DIRECT = Diabetic Retinopathy Candesartan Trial; UAER = urinary albumin excretion rate.
study were 2.5% in the candesartan group and 2.1% in the placebo group for the pooled study population. Table 4 lists the rates for the individual studies, together with serious adverse events and deaths.

**DISCUSSION**

In the DIRECT-Renal analysis, candesartan had no effect on incidence of microalbuminuria over 4.7 years in normoalbuminuric and normotensive patients with type 1 diabetes and normoalbuminuric patients with type 2 diabetes with or without treated hypertension. The adjusted rate of change in UAER, although statistically significantly lower with candesartan, was modest, and its clinical significance is uncertain.

A recent meta-analysis (searching MEDLINE from 1966 to September 2003, EMBASE from 1988 to September 2003, and the Cochrane Central Register of Controlled Trials) suggested that ACE inhibitor therapy was associated with a relative risk of 0.60 (CI, 0.43 to 0.84) for microalbuminuria, macroalbuminuria, or both in a mix of normotensive and hypertensive type 1 and type 2 diabetic patients who were normoalbuminuric at baseline (15). Our study had more patients and events than this meta-analysis, but we found a nonsignificant reduction of 5% in risk for microalbuminuria with candesartan. This is substantially below the lowest end of the treatment benefit spectrum found in the meta-analysis (16%). How can we account for this discrepancy?

Of the 6 studies included in the previous meta-analysis, 3 contributed around 85% of the information: the HOPE (Heart Outcomes Prevention Evaluation) Study (16), BENEDICT (Bergamo Nephrologic Diabetic Complications Trial)
To facilitate a “like with like” comparison and include data from the recently reported ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) trial (17), we compared the characteristics and outcomes of these studies (Table 5).

The HOPE Study data presented in the published meta-analysis refer only to patients who progressed from normoalbuminuria to macroalbuminuria, reporting a beneficial treatment effect of 0.71 (15). However, the incidence of new micro- and macroalbuminuria in the 2272 diabetic patients who were normoalbuminuric at baseline in the HOPE Study was reduced by 13% in favor of the ACE inhibitor ramipril (data supplied by the HOPE Study investigators). This is substantially greater than the 8% reduction with candesartan in the type 2 diabetic patients in our study (Table 5). Similarly, BENEDICT (6) reported a 44% reduction in incidence in favor of the ACE inhibitor trandolapril for progression to microalbuminuria. Patients in the HOPE Study and BENEDICT were older and had higher systolic blood pressures than patients in DIRECT-Renal (11 mm Hg greater than that in hypertensive patients receiving treatment and 32 mm Hg greater than that in normotensive type 2 diabetic patients). These differences may reflect greater RAS activity, which might make patients more responsive to RAS blockade. The ADVANCE trial (17) also observed a significantly reduced incidence of microalbuminuria of 17% for the ACE inhibitor perindopril, but these patients, like those in HOPE Study and BENEDICT, were at substantially greater risk for cardiovascular disease than those recruited to DIRECT-Renal, which might explain the small observed absolute risk reduction of 5.5% (Table 5). We therefore suggest that the base-

<table>
<thead>
<tr>
<th>Variable</th>
<th>DIRECT-Prevent 1</th>
<th>EUCLID (8)</th>
<th>DIRECT-Protect 1</th>
<th>HOPE Study (16)*</th>
<th>BENEDICT (6)</th>
<th>ADVANCE (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety population</td>
<td>710 (71)</td>
<td>517 (73)</td>
<td>951 (78)</td>
<td>721 (76)</td>
<td>796 (84)</td>
<td>786 (83)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>505 (71)</td>
<td>517 (73)</td>
<td>738 (78)</td>
<td>721 (76)</td>
<td>796 (84)</td>
<td>786 (83)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>102 (14)</td>
<td>117 (17)</td>
<td>133 (14)</td>
<td>138 (15)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>97 (14)</td>
<td>95 (13)</td>
<td>119 (13)</td>
<td>140 (15)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>105 (15)</td>
<td>59 (8)</td>
<td>107 (11)</td>
<td>45 (5)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>53 (7)</td>
<td>73 (10)</td>
<td>112 (12)</td>
<td>104 (11)</td>
<td>79 (8)</td>
<td>94 (10)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>124 (13)</td>
<td>173 (18)</td>
</tr>
<tr>
<td>Influenza</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>77 (8)</td>
<td>83 (9)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>79 (8)</td>
<td>79 (8)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>11 (2)</td>
<td>9 (1)</td>
<td>14 (2)</td>
<td>17 (2)</td>
<td>41 (4)</td>
<td>30 (3)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>102 (14)</td>
<td>112 (16)</td>
<td>173 (18)</td>
<td>161 (17)</td>
<td>301 (32)</td>
<td>267 (28)</td>
</tr>
<tr>
<td>Discontinuation due to adverse event</td>
<td>22 (3)</td>
<td>18 (3)</td>
<td>17 (2)</td>
<td>16 (2)</td>
<td>37 (4)</td>
<td>42 (4)</td>
</tr>
<tr>
<td>Deaths</td>
<td>7 (1)</td>
<td>5 (1)</td>
<td>7 (1)</td>
<td>8 (1)</td>
<td>37 (4)</td>
<td>35 (4)</td>
</tr>
</tbody>
</table>

DIRECT = Diabetic Retinopathy Candesartan Trial.

* Data are reported as the number (percentage) of patients who had at least 1 adverse event. The 4 most common adverse events per study are presented, as well as hyperkalemia (reported as an adverse event), serious adverse events, discontinuations, and deaths.
line burden of vasculopathy (possibly a reflection of increased vascular RAS activity) may determine the response to RAS blockade in type 2 diabetes—the higher it is, the greater the effect.

The EUCLID (7) trial included patients with type 1 diabetes whose baseline UAER was greater than 5 µg/min (the median for DIRECT-Renal) in more than 70% of all patients, and the treatment effect of the ACE inhibitor lisinopril was observed in this subgroup alone. Our results for type 1 diabetes are completely consistent with previously published data (15).

As such, our data might question the orthodoxy of a definite benefit of RAS blockade in the primary prevention of diabetic nephropathy for all patients. However, important aspects of DIRECT-Renal need to be considered before reaching this conclusion. First, the study was not powered for a renal end point. Second, the microalbuminuria event rate in DIRECT-Renal was lower than that in many previously published studies (18–21), particularly for the patients with type 1 diabetes. In the DCCT, which used a single 4-hour timed collection (4), approximately 12% of the conventional treatment group in the primary prevention cohort (similar to the DIRECT-Prevent 1 sample) and 23% of the conventional treatment group in the secondary prevention cohort (similar to the DIRECT-Protect 1 sample) had a UAER greater than 28 µg/min at 4 years (compared with 0.5% and 1.6% in the placebo groups in DIRECT-Prevent 1 and DIRECT-Protect 1, respectively). For the patients with type 2 diabetes in DIRECT-Renal, however, the event rate (14.8%) was more similar to that in BENEDICT (10.0%), but was considerably less than that in the HOPE Study (38.2%) and the ADVANCE trial (19.6%) for the placebo groups. The higher rates in the HOPE Study and the ADVANCE trial might be a reflection of the stringency of the diagnosis, because both studies used a single urinary albumin–creatinine ratio (with a very low threshold [2 mg/mmol in the HOPE Study]) at only 2 time points over the duration of the trials, whereas DIRECT-Renal and BENEDICT used multiple timed collections at 12- and 6-month intervals, respectively.

The overall median baseline UAER of 5 µg/min in DIRECT-Renal is low. The rate of change in UAER from baseline may be so slow that the ability to detect an effect of treatment over 4.7 years would be limited. Moreover, many of these patients may never develop nephropathy—the cumulative incidence in type 1 diabetes is only 40% after 40 years (22) and may be decreasing, although most will show some retinopathy after this time (23).

Candesartan might not be as effective at blocking the RAS as an ACE inhibitor. The dosage of candesartan we used was 32 mg/d, and good blockade of the RAS has been demonstrated at this level (24). Moreover, angiotensin-receptor blockers have been shown to be highly effective in reducing progression of established diabetic nephropathy (25–27); therefore, it is unlikely that they would be less effective than ACE inhibitors in normoalbuminuric patients, and our results are consistent with EUCLID for type 1 diabetes. The clinical characteristics of the patients who developed microalbuminuria compared with those of patients who did not were similar to those previously published (18–21), so it is unlikely that the DIRECT-Renal study samples were in some way atypical.

The treatment effect of candesartan on the rate of change in UAER was clinically small. Such a modest reduction might result in a long-term clinical benefit for patients, but a much longer duration of follow-up would be necessary to confirm any effect.

We believe that DIRECT-Renal is the largest trial to date to address the question of the role of RAS blockade in preventing microalbuminuria in normoalbuminuric, mostly normotensive people with diabetes. In this patient sample with a low burden of vasculopathy, we could not show a beneficial effect of candesartan therapy on microalbuminuria prevention over 4.7 years. Studies of RAS blockade in diabetic patients with low vascular burden probably require much longer follow-up to establish whether it offers clinically beneficial treatment in the primary prevention of cardiorenal complications. A meta-analysis of individual patient data from the major studies might help to resolve this question, but our results would not support the use of candesartan or other RAS-blocking agents in the primary prevention of diabetic nephropathy in patients with type 1 diabetes or in patients with type 2 diabetes and a low vascular burden.

From Newcastle University, Newcastle upon Tyne, United Kingdom; South Tees Hospitals NHS Trust and James Cook University Hospital, Middlesbrough, United Kingdom; International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College Healthcare NHS Trust, and University College London, London, United Kingdom; Odense University Hospital, Odense, Denmark; University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; University of Pittsburgh, Pittsburgh, Pennsylvania; University of Turin, Turin, Italy; and Rigshospitalet, University of Copenhagen, and Aarhus University, Copenhagen, Denmark.

The results were presented at the 44th Annual Meeting of the European Association for the Study of Diabetes, Rome, Italy, 7–11 September 2008, and at the American Society of Nephrology Renal Week, Philadelphia, Pennsylvania, 4–9 November 2008.

Acknowledgment: The authors thank the HOPE Study investigators for supplying the unpublished data in Table 5.

Grant Support: By AstraZeneca and Takeda.

Candesartan and Prevention of Microalbuminuria in Diabetes

(AstraZeneca, Takeda), A.K. Sjolie (AstraZeneca, Takeda), J. Fuller (Takeda, AstraZeneca), R. Klein (AstraZeneca, Lilly, Novartis, Pfizer), T. Orchard (AstraZeneca, Takeda), M. Porta (AstraZeneca, Takeda), H.H. Parving (Novartis, Merck & Co., Pfizer, Sanofi-Aventis, AstraZeneca). Stock ownership or options (other than mutual funds): T. Orchard (Bristol-Myers Squibb), H.H. Parving (Merck & Co., Novo Nordisk). Members of the steering committee received an annual honorarium/consultancy fee from the funding companies (AstraZeneca and Takeda).

Reproducible Research Statement: Study protocol: A description of the protocol has been published (10). The full version is available at www.clinicaltrials.gov. Statistical code: Not available. Data set: Main results (but not individual data) are available at www.direct-results.org.

Requests for Single Reprints: Rudy Bilous, MD, James Cook University, Marton Road, Middlesbrough TS4 3BW, United Kingdom; e-mail, rudy.bilous@stees.nhs.uk.

Current author addresses and author contributions are available at www.analogs.org.

References

CURRENT AUTHOR ADDRESSES: Dr. Bilous: Newcastle University, South Tees Hospitals NHS Trust, Academic Centre, James Cook University Hospital, Marton Road, Middlesbrough TS4 3BW, United Kingdom. Dr. Chaturvedi: Middlesbrough University Hospital, Department of Clinical Ophthalmology, United Kingdom. Dr. Fuller: Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, United Kingdom. Dr. Klein: Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, University Avenue, Madison, WI 53726. Dr. Orchard: Graduate School of Public Health, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA 15213. Dr. Porta: Department of Internal Medicine, University of Turin, Corso AM Dogliotti, I-10126 Turin, Italy. Dr. Parving: Rigshospitalet, Department of Medical Endocrinology, University of Copenhagen, Blegdamsvej 9, DK 2100, Copenhagen, Denmark.


APPENDIX

DIRECT Program Study Group

DIRECT Steering Committee: Anne Katrin Sjølie, Chair (Odense, Denmark); Rudy Bilous (Middlesbrough, United Kingdom); Nish Chaturvedi (London, United Kingdom); Yvonne Fox (Gothenburg, Sweden); John Fuller (London, United Kingdom); Michael George (London, United Kingdom); Anders Svensson (Gothenburg, Sweden); until August 2007); James Hainer (Princeton, New Jersey; from September 2007); Ronald Klein (Madison, Wisconsin); Trevor Orchard (Pittsburgh, Pennsylvania); Hans-Henrik Parving (Copenhagen, Denmark); Massimo Porta (Turin, Italy); Ingrid Warnold (Gothenburg, Sweden).

International Coordinators Group: Carl-David Agardh, Sweden; Rudy Bilous, United Kingdom; Francois Bonnici, South Africa; Bernard Charbonnel, France; Mark Cooper, Australia; Ivan Dedov, Russia; Robert Gardiner, Canada; Ramon Gomis, Spain; Hasan Ilkova, Turkey; Nicholas Katsilambros, Greece; Zsuzsa Kerenyi, Hungary; Stephan Martin, Germany; Pascale Massin, France; Valdis Pirags, Baltic states; Massimo Porta, Italy; Itamar Raz, Israel; Zdenek Rusavy, Czech Republic; Guntram Scherthanher, Austria; Marina Shestakova, Russia; Anne Katrin Sjølie, Denmark; Krzysztof Strojek, Poland.


Independent statisticians: Hans Wedel (Gothenburg, Sweden).

Independent Safety Committee: Lars Wilhelmsen, Chair (Gothenburg, Sweden); Alan Bird (London, United Kingdom); Hans Wedel (Gothenburg, Sweden).

DIRECT Project Team: Ingrid Warnold, Project Leader (AstraZeneca, Gothenburg, Sweden); Graham Price, Deputy Project Leader (Takeda, London, United Kingdom); Elisabeth Adler-Ekholm (AstraZeneca, Gothenburg, Sweden); Stephen Aldington (Retinopathy Grading Centre, London, United Kingdom); Magnus Dahl (AstraZeneca, Gothenburg, Sweden); Aaron Deveney (Takeda, London, United Kingdom); Eva Karlsten (AstraZeneca, Gothenburg, Sweden); Philippa Levins (ICON, Dublin, Ireland); Helen Lipinski (Retinopathy Grading Centre, London, United Kingdom); Carol Prenter (ICON, Dublin, Ireland); Helen Walkey (Academic Coordinating Centre, London, United Kingdom); Nicola Walters (Quest, London, United Kingdom).

DIRECT Investigators

Australia: Mark Cooper (National Coordinator), Roger Chen, Peter Colman, Peter Davoren, Thomas Donnelly, Michael d’Emden, George Jerums, Richard O’Brien, Pat Phillips, John Prins, Anthony Roberts, Gerald Watts, Dennis Wilson, Dennis Yue, Sophia Zoungas.

Austria: Guntram Scherthanher (National Coordinator), Anton Lugner, Ernst Pilger, Rudolf Prager, Werner Klaus Waldhäusl, Raimund Weitgasser.

Belgium: Bart Keymeulen, Luc Van Gaal.


Canada: Robert Gardiner (National Coordinator), Sandra Babin, Andre Belanger, Chantal Godin, Carol Joyce, Erin Keely, Lawrence Leiter, Heather Lochman, Ruth McManus, David Miller, Theodore Monchesky, George Pylypchuk, Stuart Ross, Irving Siegel, Sheldon Tobe, Ehud Ur, Vincent Woo, Ellen Toth.

Croatia: Damir Kovacevic, Velimir Prozovic.

Czech Republic: Zdenek Rusavy (National Coordinator), Michal Andel, Petr Boucek, Petr Chmura, Anna Gregorova, Jana Havelkova, Jaroslava Karasova, Frantisek Musil, Jindrich Olsovsky, Frantisek Patek, Blanka Plesnikova, Yvona Pospisilova, Eva Racicka, Jana Zawadova.


Estonia: Valdis Pirags (National Coordinator), Marju Past, Hiie Tups, Toomas Podar.

Georgia: Nino Gagunashvili, Ramaz Kurashvili, David Metreveli.

Germany: Stephan Martin (National Coordinator), Bruno Allolio, Helmut Anderten, Klaus Badenhoop, Klaus Busch, Manfred Dreyer, Harald Etzrodt, Matthias Frank, Andreas Hamann, Hans-Peter Hamme, Hans-Peter Kempe, Raimund Konzok, Ulrich Alfons Mueller, Ralf Paschke, Matthias Pein, Andreas Pfeiffer, Ernst-Otto von Reis, Michael Schneider, Andreas Schäffler, Werner Steurer, Klaus-Henning Usadel.

Greece: Nicholas Katsilambros (National Coordinator), Basil Karamanos, Andreas Melidonis, Ilias Mygdalis, Marina Noutsou, Emanuel Pagalos, Andreas Papadam, Angelos Pappas, Stavros Pappas, Konstantinos Phenekos, Georgios Piaditis.


Ireland: Barry Ferriss, Joseph McKenna, Donal O’Shea, Sheila O’Sullivan.


Italy: Massimo Porta (National Coordinator), Luciano Corgiat-Mansin, Rita Leoncavallo Gaetano Crepaldi, Aldo Galluzzo, Giovanni Ghirlanda, Cecilia Iniviti, Claudio Noacco, Piermarco Piatti, Giuseppe Realdi, Franco Saccardi, Fausto Santensiano, Giorgio Luciano Viviani.

Latvia: Valdis Pirags (National Coordinator), Baiba Jegere, Guna Laganovska, Ingvars Rasa, Irina Vinsteine.

Lithuania: Valdis Pirags (National Coordinator), Juzas Dainiucius, Antanas Norkus, Rimantas Zalinkevičius.

Luxembourg: Georges Michel, Roger Wirion.

New Zealand: Paul Drury, Peter Dunn, Russel Scott, Robyn Toomath.

Poland: Krzysztof Strojek (National Coordinator), Elzbieta Bandurska-Stankiewicz, Barbara Idziour-Walus, Waldemar Karnafel, Malgorzata Kozioł, Ewa Krzyzogorska, Jerzy Lopatynski, Krzysztof Markiewicz, Anna Mikolajczyk-Swatko, Maria Emilia Józefowska, Maria Niedzielska, Stanisław Polaszewski, Slawomir Pynka, Ewa Semetkowska-Jurkiewicz.

Portugal: Luis Gardete, Manuel Joao Gomes, Arnaldo Sa.

Romania: Monica Liliana Angelescu, Mariana Graur, Maria Mota, Gina Camelia Suciu, Constantin Ionescu Tirgoviste, Andrei Ioan Veresiu.


Spain: Ramon Gomis (National Coordinator), Ramon Albero, Alfonso Gentil Baldrich, Juan José Barberia Layana, Fernando Gomez Peralta, Olga Gonzalez Albarrán, Forga Louis, Anna Novials Sarda, Francesco Pinon-Selles.

Sweden: Carl-David Agardh (National Coordinator), Ulf Adamson, Elisabet Agardh, Michael Alvarsson, Ibe Lager, Stina Lindmark, Anders Nilsson, Bengt Norberg, Maria Svensson.

Turkey: Hasan Ilkova (National Coordinator), Yalcin Aral, Goksun Ayvaz, Nilgun Baskal, Selcuk Dagdelen, Gurbuz Erdogan, Ahmet Kaya, Fulya Tanyeri, Candegger Yilmaz.