

Effect of Candesartan on Microalbuminuria and Albumin Excretion Rate in Diabetes

Three Randomized Trials

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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 $\mu\text{g}/\text{min}$).

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 $\mu\text{g}/\text{min}$ 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 $\mu\text{g}/\text{min}$). 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.

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* 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).

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Microalbuminuria in diabetes, defined as a urinary albumin excretion rate (UAER) of 20 $\mu\text{g}/\text{min}$ or greater, is strongly predictive not only of nephropathy and end-stage renal disease (1) but also of premature cardiovascular morbidity and mortality (2, 3). Effective preventive therapies are therefore a clinical priority.

Both the DCCT (Diabetes Control and Complications Trial) in type 1 diabetes (4) and UKPDS (United Kingdom Prospective Diabetes Study) in type 2 diabetes (5) have demonstrated the effectiveness of intensive glyce-mic control on prevention of microalbuminuria. However, this is not always easy to achieve, and nephropathy continues to occur, leaving an unmet need for definitive trials of primary prevention of microalbuminuria. Renin-angiotensin system (RAS) blockade once nephropathy is established is now almost universal practice, but whether it is beneficial at an earlier stage is uncertain. The angiotensin-converting enzyme (ACE) inhibitor trandolapril reduced progression to microalbuminuria in type 2 diabetic patients with established hypertension, but whether this would also be true in normotensive persons is not known (6). In type 1 diabetes, EUCLID (Eurodiab Controlled Trial of Lisinapril in

Insulin-Dependent Diabetes) (7) reported a large but statistically nonsignificant effect of RAS blockade on progression to microalbuminuria in normotensive persons. Although these previous findings are promising, the role of RAS blockade in normoalbuminuric persons with diabetes remains unclear.

The DIRECT (Diabetic Retinopathy Candesartan Trials) Program was set up to investigate whether the angiotensin-receptor blocker candesartan could prevent development or progression of diabetic retinopathy in nor-

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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 \leq 130/85 mm Hg) and normoalbuminuric (UAER $<$ 20 μ g/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 \leq 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 ste-

notic 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 \geq 110 μ mol/L [\geq 1.2 mg/dL] in women and \geq 130 μ mol/L [\geq 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 A_{1c} (HbA_{1c}) (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 μ g/L, with a maximum allowable coefficient of variation of 5% in the mean range of 50 to 100 μ g/L.

We asked patients who developed microalbuminuria (UAER \geq 20 μ g/min) in 1 or both urine samples at any time to provide 2 more samples. If 3 or 4 of these 4 con-

secutive 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.

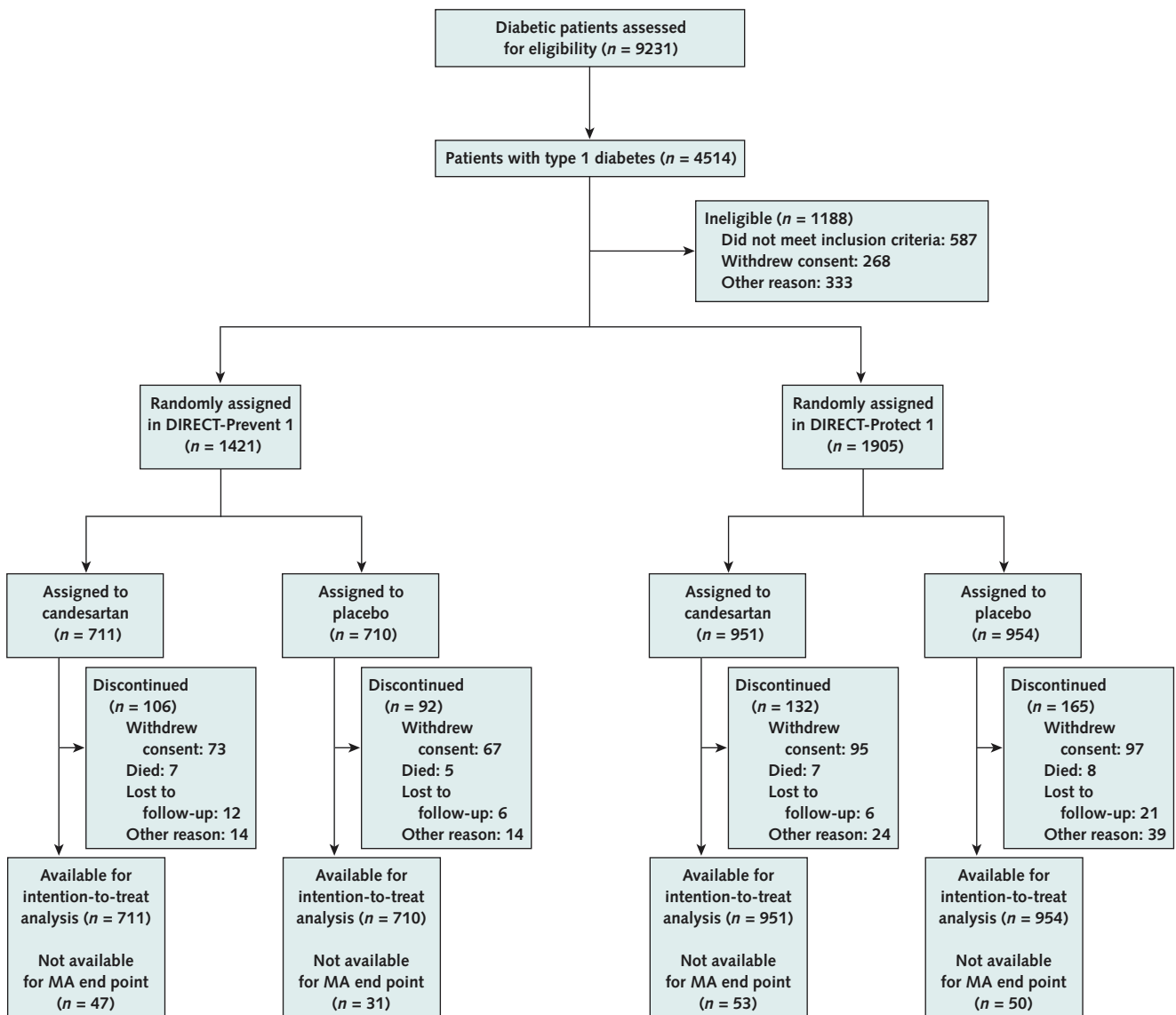
Measurements and Outcomes

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

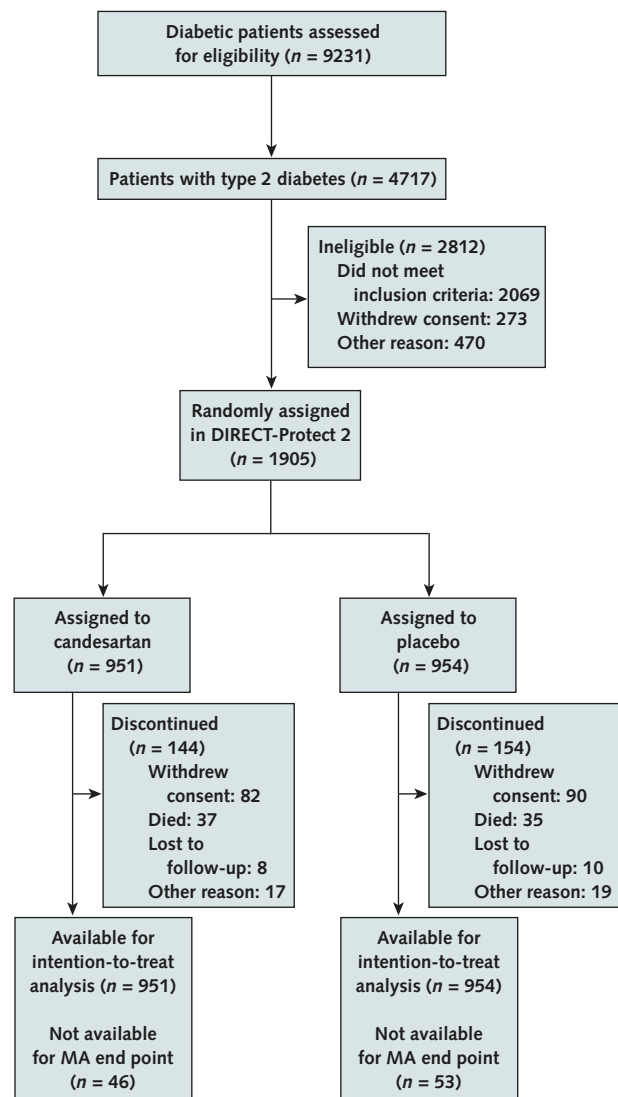
A steering committee of senior investigators and representatives of the funding companies oversaw the study. ICON (Dublin, Ireland) did site monitoring to standard

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.

Figure 2. Study flow diagram for patients with type 2 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 micro-

albuminuria 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, HbA_{1c}, 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, HbA_{1c} 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 A_{1c} levels and smoking rates were similar in the 3 studies. Serum cholesterol levels were slightly higher in DIRECT-

Protect 2 than in the studies of type 1 diabetes, but only 5% of patients had a history of myocardial infarction. Notably, UAER was low (median <5.0 μg/min) in the 3 studies.

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 median 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

Table 1. Baseline Patient Characteristics

Variable	DIRECT-Prevent 1		DIRECT-Protect 1		DIRECT-Protect 2		Pooled DIRECT Studies	
	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo
Patients, n	711	710	951	954	951	954	2613	2618
Mean age (SD), y	29.6 (8.0)	29.9 (8.1)	35.1 (8.5)	31.9 (8.5)	56.9 (7.6)	56.8 (7.9)	40.2 (15)	40.5 (14.9)
Male, n (%)	413 (58)	392 (55)	538 (57)	553 (58)	466 (49)	482 (51)	1417 (54)	1427 (55)
White, n (%)	690 (97)	685 (97)	928 (98)	943 (99)	916 (96)	914 (96)	2534 (97)	2542 (97)
Mean duration of diabetes (SD), y	6.6 (3.9)	6.8 (3.9)	10.9 (4.3)	11.0 (4.3)	8.8 (4.9)	8.7 (4.8)	9.0 (4.7)	9.1 (4.7)
Mean HbA _{1c} level (SD)*	8.0 (1.7)	8.2 (1.7)	8.5 (1.76)	8.5 (1.6)	8.2 (1.6)	8.2 (1.6)	8.3 (1.6)	8.3 (1.6)
Treated for hypertension, n (%)	2 (0.3)	0	2 (0.2)	0	588 (62)	592 (62)	590 (23)	594 (23)
β-Blocker	1 (0.1)	0	1 (0.1)	0	234 (25)	242 (25)	236 (40)	242 (41)
Diuretic	0	0	1 (0.1)	0	183 (19)	172 (18)	184 (31)	172 (29)
Calcium-channel blocker	1 (0.1)	0	0	0	156 (16)	168 (18)	157 (27)	168 (28)
Mean SBP (SD), mm Hg†	116 (9.5)	116 (9.6)	117 (9.6)	117 (9.8)	123 (8.7)	123 (9.0)	118 (9.8)	118 (9.9)
Mean SBP with antihypertensive medication (type 2 diabetes only) (SD), mm Hg	–	–	–	–	139 (12.7)	139 (12.0)	139 (12.7)	139 (12.0)
Mean DBP (SD), mm Hg†	72 (6.9)	72 (7.3)	74 (6.5)	73 (6.5)	75 (6.4)	76 (6.5)	74 (6.7)	73 (7.1)
Mean DBP with antihypertensive medication (type 2 diabetes only) (SD), mm Hg	–	–	–	–	79 (6.9)	80 (7.1)	79 (6.9)	80 (7.1)
Smoker, n								
Never	490	471	610	630	698	695	1798	1796
Former	50	47	81	81	121	112	252	240
Current	171	192	260	243	132	147	563	582
Mean BMI (SD), kg/m ²	23.8 (3.2)	24.1 (3.5)	24.7 (3.7)	24.6 (3.5)	29.4 (4.6)	29.4 (4.8)	26.2 (4.7)	26.2 (4.7)
Mean total cholesterol level (SD)								
mmol/L	4.7 (1.0)	4.8 (1.1)	4.8 (0.9)	4.8 (0.9)	5.3 (1.1)	5.3 (1.1)	5.0 (1.0)	5.0 (1.1)
mg/dL	181 (39)	185 (42)	185 (35)	185 (35)	205 (42)	205 (42)	193 (39)	193 (42)
Mean HDL cholesterol level (SD)								
mmol/L	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)	1.4 (0.3)	1.4 (0.3)	1.6 (0.4)	1.6 (0.4)
mg/dL	66 (15)	66 (15)	66 (15)	66 (15)	54 (12)	54 (12)	62 (15)	62 (15)
Mean serum creatinine level (SD)								
μmol/L	90.5 (13.6)	89.7 (13.6)	90.2 (13.2)	91.3 (13.4)	90.3 (15.6)	90.1 (15.2)	90.3 (14.2)	90.4 (14.2)
mg/dL	1.0 (0.2)	1.0 (0.2)	1.0 (0.1)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)
Mean serum potassium level (SD), mmol/L	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)
Median UAER (25th, 75th percentiles), μg/min	4.5 (3.0, 6.5)	4.5 (3.0, 7.0)	5.0 (3.5, 7.0)	5.0 (3.5, 7.5)	5.5 (3.5, 8.5)	5.5 (3.5, 8.5)	5.0 (3.5, 7.5)	5.0 (3.5, 7.5)

BMI = body mass index; DBP = diastolic blood pressure; DIRECT = Diabetic Retinopathy Candesartan Trial; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; SBP = systolic blood pressure; UAER = urinary albumin excretion rate.

* Aligned to DCCT (Diabetes Control and Complications Trial) standards.

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

Table 2. Incidence of Microalbuminuria and Annual Change in UAER

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

DIRECT = Diabetic Retinopathy Candesartan Trial; UAER = urinary albumin excretion rate.

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 ($P < 0.005$). 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.

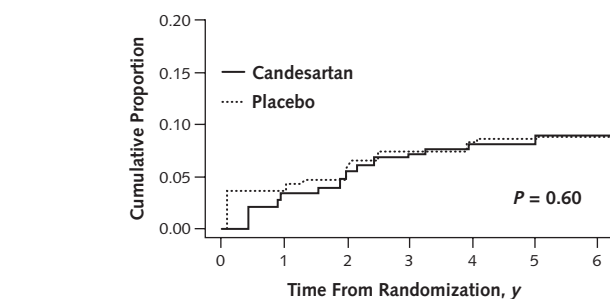
Table 3 shows the cumulative percentage of patients who developed microalbuminuria in each study (separating the hypertensive and normotensive patients in DIRECT-Protect 2). The percentage of patients who began open-label RAS-blocker therapy and the median UAER are also included. The number of patients 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- $\mu\text{g}/\text{min}$ 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 HbA_{1c} 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 $\mu\text{g}/\text{min}$.

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

Figure 3. Cumulative proportion of patients with microalbuminuria.



At risk, n	0	1	2	3	4	5	6
Placebo	2618	2410	2247	2092	1754	526	15
Candesartan	2613	2426	2278	2150	1793	540	13

Table 3. Life-Table Summary of Time to Microalbuminuria in the Intention-to-Treat Sample, by Study and Antihypertensive Therapy at Baseline*

Study	Interval Year		Candesartan				Placebo			
	Start	End	At Risk for MA, n†	Cumulative Patients With MA, %	Cumulative Patients Receiving RAS Blocker, %‡	Median UAER, µg/min§	At Risk for MA, n†	Cumulative Patients With MA, %	Cumulative Patients Receiving RAS Blocker, %‡	Median UAER, µg/min§
DIRECT-Prevent 1										
Baseline hypertension										
No	0	1	711	0.44	0.00	4.5	710	1.01	0.73	4.5
No	1	2	657	1.52	0.93	4.5	660	1.63	2.59	4.5
No	2	3	623	2.01	1.75	4.5	616	1.79	3.75	4.5
No	3	4	593	2.56	2.31	4.5	583	2.32	5.42	4.5
No	4	5	475	2.56	3.31	4	489	2.32	7.03	4
No	5	6	125	2.56	3.31	4.5	126	2.32	8.54	4
DIRECT-Protect 1										
Baseline hypertension										
No	0	1	951	2.93	0.11	5	954	3.04	0.66	5
No	1	2	864	4.93	0.35	5	856	4.58	1.98	5
No	2	3	819	6.28	0.97	5	798	6.21	4.19	5
No	3	4	778	7.36	2.20	5	728	7.05	5.35	5
No	4	5	677	7.36	3.07	4.5	643	7.26	5.57	4.5
No	5	6	242	7.36	3.87	5	240	7.26	7.20	5
DIRECT-Protect 2										
Baseline hypertension										
No	0	1	363	3.69	4.05	5	362	6.57	1.18	5
No	1	2	314	6.17	6.01	6	312	11.47	5.21	5.5
No	2	3	292	9.47	8.88	6	271	15.04	11.64	5.5
No	3	4	259	11.36	12.22	5.5	241	16.68	16.19	6
No	4	5	211	13.94	13.70	5.5	189	16.68	18.61	6
No	5	6	57	13.94	13.70	5	56	16.68	18.61	6.5
Yes	0	1	588	6.99	4.51	5.5	592	6.13	8.66	5.5
Yes	1	2	496	10.54	10.55	5.5	468	9.48	16.81	6.5
Yes	2	3	435	13.08	14.82	5.5	403	12.89	22.80	6
Yes	3	4	390	14.50	19.78	6.25	342	14.38	30.12	6
Yes	4	5	318	15.34	26.31	5.5	264	15.30	37.04	6.25
Yes	5	6	67	15.34	29.21	6	43	15.30	41.48	6.25

DIRECT = Diabetic Retinopathy Candesartan Trial; MA = microalbuminuria; RAS = renin-angiotensin system; UAER = urinary albumin excretion rate.

* Using midpoint approximation of time to event.

† Number at risk at start of interval.

‡ Patients whose first intake of RAS blocker was after an MA event were censored at the time of the MA event.

§ Including patients with events in all intervals up to study discontinuation.

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 Septem-

ber 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), BENE-DICT (Bergamo Nephrologic Diabetic Complications Trial)

Table 4. Adverse Events*

Variable	DIRECT-Prevent 1		DIRECT-Protect 1		DIRECT-Protect 2	
	Candesartan	Placebo	Candesartan	Placebo	Candesartan	Placebo
Safety population	710	710	951	951	949	953
Any adverse event	505 (71)	517 (73)	738 (78)	721 (76)	796 (84)	786 (83)
Nasopharyngitis	102 (14)	117 (17)	133 (14)	138 (15)	–	–
Hypoglycemia	97 (14)	95 (13)	119 (13)	140 (15)	–	–
Hypotension	105 (15)	59 (8)	107 (11)	45 (5)	–	–
Headache	53 (7)	73 (10)	112 (12)	104 (11)	79 (8)	94 (10)
Hypertension	–	–	–	–	124 (13)	173 (18)
Influenza	–	–	–	–	77 (8)	83 (9)
Pain in extremity	–	–	–	–	79 (8)	79 (8)
Hyperkalemia	11 (2)	9 (1)	14 (2)	17 (2)	41 (4)	30 (3)
Any serious adverse event	102 (14)	112 (16)	173 (18)	161 (17)	301 (32)	267 (28)
Discontinuation due to adverse event	22 (3)	18 (3)	17 (2)	16 (2)	37 (4)	42 (4)
Deaths	7 (1)	5 (1)	7 (1)	8 (1)	37 (4)	35 (4)

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.

(6), and EUCLID (7). 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) re-

ported 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 5. Comparison of Studies in Patients With Type 1 and Type 2 Diabetes

Study	DIRECT-Prevent 1 and DIRECT-Protect 1	EUCLID (8)	DIRECT-Protect 2	HOPE Study (16)*	BENEDICT (6)	ADVANCE (17)
Patients, <i>n</i>						
Treated	1662	213	951	1170	601	3931
Placebo	1664	227	954	1102	603	3946
Type of diabetes	Type 1	Type 1	Type 2	Type 2	Type 2	Type 2
Mean age, <i>y</i>	31	331	57	65	62	66
Blood pressure, <i>mm Hg</i>	117/73	122/80	133/78	142/80	151/88	145/81
Previous ischemic heart disease, %	0	0	5	60	NA	12
Previous stroke, %	0	0	2	8	NA	9
Previous peripheral vascular disease, %	0	0	0	19	NA	NA
Active treatment	Candesartan	Lisinopril	Candesartan	Ramipril	Trandolapril	Perindopril
Duration of treatment, <i>y</i>	4.7	2.0	4.7	4.5	3.6	4.3
Incidence of new microalbuminuria (treatment vs. placebo), %	5 vs. 5	6 vs. 8	12 vs. 13	33 vs. 38	5.7 vs. 10.0	27.8 vs. 33.3

ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; BENEDICT = Bergamo Nephrologic Diabetic Complications Trial; DIRECT = Diabetic Retinopathy Candesartan Trial; EUCLID = Eurodiab Controlled Trial of Lisinopril in Insulin-Dependent Diabetes; HOPE = Heart Outcomes Prevention Evaluation; NA = not available.

* HOPE Study data in this table are previously unpublished.

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 $\mu\text{g}/\text{min}$ (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 $\mu\text{g}/\text{min}$ 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 $\mu\text{g}/\text{min}$ 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.

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Lithuania: Valdis Pirags (*National Coordinator*), Juozas Danilevicius, Antanas Norkus, Rimantas Zalinkevicius.

Luxembourg: Georges Michel, Roger Wirion.

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

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

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