Long-Term Dual Blockade With Candesartan and Lisinopril in Hypertensive Patients With Diabetes

The CALM II study

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OBJECTIVE — To assess and compare the long-term effects of the combination of candesartan and lisinopril with high-dose lisinopril on systolic blood pressure in patients with hypertension and diabetes.

RESEARCH DESIGN AND METHODS — This was a prospective, randomized, parallel-group, double-blind, double-dummy study with a 12-month follow-up. Drug therapy was either lisinopril 40 mg once daily or dual-blockade treatment with candesartan 16 mg once daily and lisinopril 20 mg once daily. The study comprised 75 type 1 and type 2 diabetic patients aged 35–74 years. The main outcome measures were seated and 24-h ambulatory systolic blood pressure.

RESULTS — Reduction in systolic blood pressure (24-h systolic blood pressure) reduction was obtained in both treatment arms (mean reduction at final follow-up: dual blockade 6 mmHg vs. lisinopril 2 mmHg), but no significant difference was found between dual-blockade and lisinopril 40 mg once daily ($P = 0.10$). Both treatments were generally well tolerated, and similar low rates of side effects were found in the two groups.

CONCLUSIONS — There was no statistically significant difference between lisinopril 40 mg once daily and lisinopril 20 mg in combination with candesartan 16 mg once daily in reducing systolic blood pressure in hypertensive patients with diabetes.

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Dual blockade of the renin-angiotensin system was opted for based on the principle of obtaining the broadest and most efficient blockade of the effects of angiotensin II by using the combination of an ACE inhibitor and an angiotensin II receptor blocker (AIIA).

By combining two different pharmacological principles and inhibiting both the ACE and the angiotensin II type 1 receptor, it seems possible to arrive at a treatment regimen that inhibits both the production and the action of angiotensin II and serves as an efficient antihypertensive therapy. The Candesartan and Lisinopril Microalbuminuria (CALM) study was among the first to show an additional effect from dual blockade on blood pressure in a population of type 2 diabetic patients with microalbuminuria over a 12-week follow-up period (1).

Following the CALM study, several small-scale studies indicated that using dual blockade in treating type 1 and type 2 diabetic patients might produce additional clinical effects on both blood pressure and albumin excretion (2–4). Moreover, one large-scale study in nondiabetic patients with nephropathy has also shown that dual-blockade treatment has an effect in the long term (5).

However, several important clinical questions remain unresolved: *1*) What are the clinical effects of dual blockade compared with an efficient dosage titration of an ACE inhibitor? *2*) Does the effect of dual blockade persist over a longer period of time? *3*) What are the long-term safety and tolerability characteristics of the two treatment regimes?

Thus, the primary objective of the CALM II study was to compare over a 12-month period the results of adding either candesartan cilexetil 16 mg or lisinopril 20 mg to concomitant antihypertensive treatment with lisinopril 20 mg in hypertensive patients with diabetes. The second objective was to assess the safety and tolerability of the two treatments.

RESEARCH DESIGN AND METHODS

— The CALM II study is a one-center, one-observer, double-blind, randomized, active-controlled, parallel-group study comprising 75 patients with diabetes and hypertension. All included patients had a seated office systolic blood

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Abbreviations: AIIA, angiotensin II receptor blocker; CALM, Candesartan and Lisonopril Microalbuminuria; UACR, urine albumin-to-creatinine ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

pressure between 120 and 160 mmHg (mean of three measurements) during treatment with lisinopril 20 mg once daily for at least 1 month before randomization. Additional treatment with other antihypertensive drugs like diuretics, calcium channel blockers, or β-blockers was allowed, as long as the dosage of these drugs was not changed during the study period.

The main exclusion criteria were *1*) age <18 and >75 years; *2*) nondiabetic cause of secondary hypertension or malignant hypertension; *3*) cardiovascular events within 6 months before randomization; *4*) impaired renal function with a serum creatinine ≥130 μmol/l or plasma potassium outside normal range; *5*) pregnancy or breast feeding.

The study was conducted in accordance with the Helsinki II declaration and was approved by the local ethics committee. All participants gave a written informed consent. The study followed the Good Clinical Practice rules and regulations. This study was conducted according to the CONSORT guidelines for clinical trials (6).

Patients were randomized to either an additional 20 mg of lisinopril in addition to concomitant lisinopril treatment (i.e., a total lisinopril dose of 40 mg once daily) or candesartan 16 mg once daily in combination with 20 mg of lisinopril once daily. The follow-up period was 12 months, with 6 visits at the clinic (after 1 week and after 1, 3, 6, 9, and 12 months). At each visit, seated blood pressure was measured at the trough level after 15 min of rest with sphygmomanometry using an appropriate cuff. Blood pressure was measured three times, after which the mean was calculated. If a patient's systolic blood pressure was above 160 mmHg or diastolic blood pressure above 90 mmHg, 2.5 mg of bendroflumethiazid was added to the patient's treatment regimen. If the blood pressure did not fall below this target level after 3–4 weeks, the patient was excluded. For safety reasons, the patient was also excluded if the systolic blood pressure fell below 110 mmHg.

Using an oscillometric technique (SpaceLabs 91207) (7), 24-h blood pressure recordings were made at baseline and after 12 months, with readings done at 20-min intervals over the course of the 24 h. Measurements were obtained during a day with normal activities at home or at work. Individually reported sleeping times were implemented in the calculation of daytime and nighttime blood pressure.

In addition, serum creatinine and potassium levels were assessed at each visit. If plasma potassium levels exceeded 6 mmol/l, a new assessment was done after 3 weeks. Then, if a further increment in plasma potassium was found, the patient was excluded.

Urinary albumin excretion

Urinary albumin excretion was assessed at baseline and at each visit subsequent to 1 month of randomized treatment. Urinary albumin-to-creatinine ratio (UACR) was determined by an immunoturbidimetric method (Roche Diagnostics, Basel, Switzerland). Because urinary albumin excretion shows a considerable intraindividual variability with a day-to-day variation of 30–50% (8), we assessed UACRs by calculating the geometric mean of three UACRs from overnight urine samples collected within 1 week at baseline and at the 12-month follow-up visit (9).

To ensure compliance at the 1-, 3-, 6-, and 9-month visits, each patient's UACR was estimated from one urine sample. In four cases (two in each group), we did not receive a urine sample at the final visit. In these cases, the result at 9 months was extrapolated to the final results. Moreover, a calculated creatinine clearance was done with the Cockroft-Gault formula ([140 − age] × body weight [kg] × K/serum creatinine [μmol/l]). K (constant) was 1.25 for men and 1.03 for women (10). A more detailed overview of the study methods employed here has already been published (11).

Statistical considerations and sample size

All data are expressed as the mean ± SD unless otherwise indicated. From previous studies, the SD of the change in systolic blood pressure measured over 24 h was estimated to be 5.7 mmHg (12). An SD of that magnitude would require a sample size of 46 completing subjects, 23 in each treatment arm, to attain a power of 90% to detect a difference of 7 mmHg to be tested at a 2-sided significance level of 1%.

Statistics related to the 24-h blood pressure values were calculated using unpaired Student's *t* tests on the Δ-values, after ensuring that these values followed the normal distribution. Repeated-measurements statistics (Hotelling's *t* test) was applied to seated blood pressure and log-transformed measurements of albuminuria, plasma potassium, and serum creatinine. For analysis of statistical significance for bivariate tabular analysis, the χ^2 test was used. All *P* values were considered significant at $P < 0.05$.

RESULTS — All patients followed the treatment protocol and were available for follow-up. Compliance was assessed by tablet counting, which showed a median of 100% (range 92–100%).

Table 1 displays the population's baseline data. With the exception of the fact that there were more patients on low-dosage thiazide treatment in the dual-blockade group, the groups were comparable.

A total of 15 patients (8 lisinopril and 7 dual blockade) had to be treated with thiazide due to insufficient blood pressure reduction. Nine of these 15 patients were excluded due to blood pressure levels that remained too high despite the addition of a thiazide, 5 belonging to the lisinopril group and 4 to the dual-blockade group.

While the dual-blockade treatment did tend to be more effective on daytime and 24-h and night systolic blood pressure, this trend was not significant. The mean differences between treatments at follow-up were as follows: daytime 5.6 mmHg (95% CI −0.4 to 11 mmHg; $P = 0.07$); nighttime 2.2 mmHg (−3.1 to 7.4 mmHg; $P = 0.40$); and 24-h systolic blood pressure 3.9 mmHg (−1.6 to 9.5 mmHg; $P = 0.16$). Patients' 24-h diastolic blood pressures remained stable in both treatment arms (Table 2).

The seated systolic blood pressure reduction was also not significantly different between the two groups (mean reduction at final follow-up: dual blockade 6 mmHg vs. lisinopril 8 mmHg). The mean difference between treatments at follow up was 0.1 mmHg (95% CI −6 to 6 mmHg; $P = 0.55$). Much like the results from the ambulatory blood pressure recordings, seated diastolic blood pressure was also unchanged at follow-up (mean reduction at final follow-up: dual blockade 0 mmHg vs. lisinopril 1mmHg; $P = 0.51$). Seated blood pressure results are shown in Fig. 1.

At baseline, we found 22 patients with normal albuminuria in the lisinopril arm and 23 in the dual-blockade arm. The remaining patients had varying degrees of

Table 1—*Baseline characteristics of patients with diabetes and hypertension.*

	Lisinopril	Dual blockade
n	37	38
Type 1 diabetes (*n*)	5	7
Age (years)	56 ± 9	54 ± 9
Female (*n*)	11	8
Systolic blood pressure (mmHg)	142.6 ± 11.0	139.1 ± 11.7
Diastolic blood pressure (mmHg)	82.8 ± 7.0	83.8 ± 10
Heart rate (bpm)	74 ± 13	72 ± 11
BMI (kg /m^2)	30 ± 5	29 ± 5
Urine albumin (mg/l)	53 (7–675)	56 (8–914)
UACR (mg/mmol)	2.0 (1–134)	2.1 (1–160)
Duration of diabetes (years)	11 (1–43)	12 (1–46)
Duration of hypertension	6.3 (1–25)	8.8 (1–30)
HbA_{1c} (%)	8.2 ± 1.3	8.4 ± 1.3
Concomitant antihypertensive treatment (*n*)		
None	21	13
Thiazide	8	20*
Calcium channel blocker	8	9
β-Blocker	5	6

Data are means ± SD and geometric mean (range), unless otherwise indicated. *$P < 0.05$ compared with the lisinopril group; χ^2 test including patients in low-dose thiazide therapy and patients without concomitant antihypertensive therapy.

albuminuria (Table 1). Not only did the urinary albumin excretion levels remain stable through the follow-up period in both groups, but we did not find significant differences in the urinary albumin excretion rate between the two regimens (mean reduction at final follow-up: dual blockade 0.42 mg/mmol vs. lisinopril 0.16 mg/mmol; $P = 0.38$) (Fig. 2).

Tolerability

Both treatments were generally well tolerated. However, three patients did experience increases in potassium, which made it necessary for them to be taken off the study medication. Of these, two patients belonged to the dual-blockade group, and one was being treated with lisinopril. One patient from each treatment group experienced fatigue and dizziness and discontinued the treatment.

Serum potassium values did not increase in the population as such (baseline 4.1 mmol/l, follow-up 4.2 mmol/l; $P = 0.87$). Serum potassium levels were not significantly different between the two groups (Table 2). Moreover, HbA_{1c} did not change significantly over time or between the two regimens during follow-up.

There were no serious drug-related events. One patient in the dual-blockade group did suffer from an infarction in the medulla oblongata associated with transient symptoms of vertigo, but the blood pressure was within the recommended levels at that time.

CONCLUSIONS

—The CALM II study is currently the study with the longest follow-up regarding dual blockade in diabetic patients. In a group of hypertensive patients with varying degrees of albuminuria, we found significant blood pressure reduction with dual blockade. However, this reduction was similar to what was obtainable with a dosage up-titration with the ACE-inhibitor lisinopril. In addition, both treatments had comparable effects on the urine albumin excretion rate within the groups. Notably, both treatments were able to stabilize the patients' UACR throughout the follow-up period, postponing the natural history of progression of diabetic nephropathy (13).

Table 2—*Effect of candesartan 16 mg once daily and lisinopril 20 mg daily compared with 40 mg lisinopril on ambulatory blood pressure and renal function in 75 hypertensive patients with diabetes*

	Dual blockade		Lisinopril 40 mg		
	Baseline	12 months	Baseline	12 months	*P* value
n	38	30	37	30	
Systolic ABP (mmHg)					
24 h	129 ± 12	123 ± 13	130 ± 11	128 ± 14	0.16
Day	134 ± 12	127 ± 13	135 ± 10	133 ± 14	0.07
Night	120 ± 15	114 ± 14	120 ± 13	117 ± 15	0.40
Night/day blood pressure ratio (%)	90 ± 7	90 ± 7	90 ± 7	87 ± 7	0.18
Diastolic ABP (mmHg)					
24 h	75 ± 8	73 ± 7	76 ± 7	74 ± 8	0.42
Day	79 ± 8	77 ± 8	80 ± 7	78 ± 9	0.55
Night	68 ± 9	65 ± 9	67 ± 9	64 ± 8	0.51
Night/day blood prssure ratio	86 ± 9	86 ± 1	83 ± 7	83 ± 7	0.83
Serum creatinine (μmol/l)	84 ± 13	86 ± 15	84 ± 15	89 ± 17	0.66
Serum potassium (mmol/l)	4.1 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.5	0.42
Creatinine clearance (ml/min)	111 ± 30	114 ± 32	110 ± 50	119 ± 30	0.65
HbA_{1c} (%)	8.2 ± 1.3	8.0 ± 1.6	8.4 ± 1.3	8.6 ± 1.7	0.59

Data are means ±SD. ABP, ambulatory blood pressure.

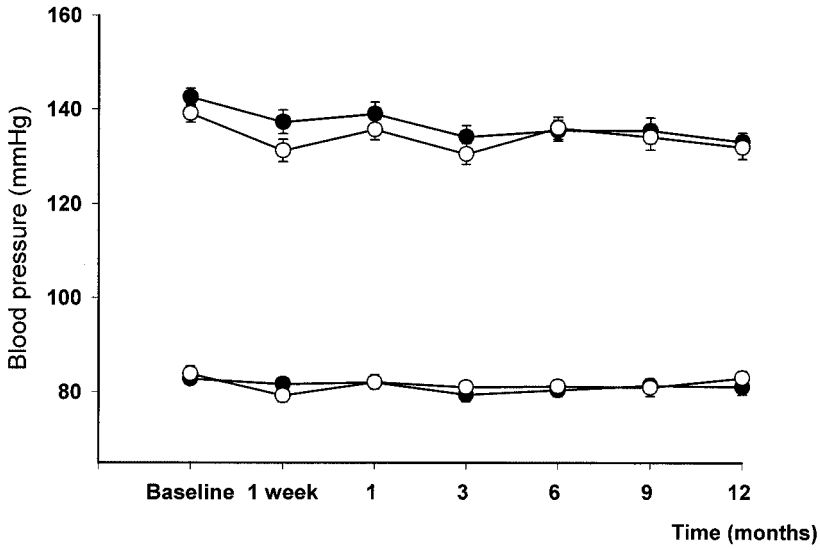

Figure 1—*Seated systolic and diastolic blood pressure recordings from baseline to follow-up.* ○, *dual blockade group;* ●, *lisinopril group.* P = *0.55. Error bars indicate SEM.*

At baseline, a significantly higher number of patients in the dual-blockade group were treated with a low dose of thiazide. Whether this skewed distribution influenced the results can only be speculated. The combination of a thiazide and an AIIA seems to have additional blood pressure lowering effects compared with monotheraphy (14,15). Conversely, the dual-blockade group could also have more severe hypertension at baseline compared with the lisinopril group, demanding more treatment. Nevertheless, a similar number of patients in the two groups needed additional antihypertensive therapy to obtain significant blood pressure reduction, and a similar proportion of patients in the two groups had to be excluded due to persistently elevated blood pressure.

It is important to emphasize that the dual-blockade treatment was equally safe and was tolerated just as well as a higher dosage of ACE inhibitor and that there were similarly few incidences of side effects in the two regimens. An increment in serum potassium, which has previously been described with dual blockade (3), was also seen in this study, but not to an extent beyond that was observed with a higher dose of lisinopril. Thus, it seems that similar precautions should be taken with dual blockade and higher-dosage ACE inhibitor treatment.

HbA_{1c} was also unchanged in the dual-blockade group, in contrast to previous observations in which dual blockade seemed to increase HbA_{1c} levels, probably as a result of a small but significant decline in hemoglobin (16).

The main rationale behind combining an ACE inhibitor with an AIIA is mainly based upon the issue of ACE escape, a mechanism where levels of angiotensin II and aldosterone return to pretreatment levels despite continuous treatment with an ACE inhibitor (17,18). It was reasoned that combining the two drugs would diminish the ACE escape phenomenon while preserving the effect on bradykinin degradation from the ACE inhibitor. Additional effects on blood pressure and neurohumoral activation from dual blockade have been observed in both clinical and experimental settings, indicating that such treatment can more appreciably inhibit the effects of angiotensin II than treatment with a fixed dose of an ACE inhibitor (19,20).

Several studies support the assertion that an appropriate dosage increment of ACE inhibitor will exert clinically relevant effects on blood pressure and outcome (21,22), effects that could equal the benefit of an additional blocking of the angiotensin II receptor. This has not been investigated until now because all previous studies have compared dual blockade with a placebo without a dosage increment of ACE inhibitor in the competing arm (1–3,23).

However, in two recently published studies where dual blockade was added to maximal recommended doses of ACE inhibitor, significant additional effects on blood pressure and proteinuria were obtained in both patients with type 1 and type 2 diabetes (16,24). Whether this can also be achieved with an even higher dose of ACE inhibitor should be investigated (22).

In conclusion, there was no statistically significant difference between lisinopril 40 mg once daily and lisinopril 20 mg in combination with candesartan 16 mg once daily in reducing systolic blood pressure in hypertensive patients with diabetes. The two treatment regimens had

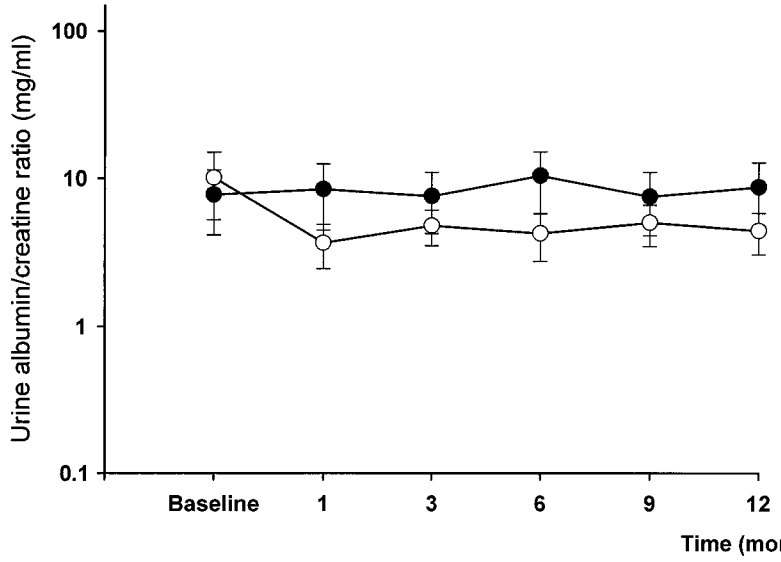

Figure 2—*UACR displayed on a log scale.* ○, *dual blockade group;* ●, *lisinopril group.* P = *0.38. Error bars indicate SEM.*

similar effects on urine albumin excretion and a similarly low incidence of side effects.

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