# Factors Determining the Blood Pressure Response to Enalapril and Nifedipine in Hypertension Associated With NIDDM

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**OBJECTIVE** — To examine the factors that determine the blood pressure response to enalapril and nifedipine monotherapy in the treatment of hypertension associated with non-insulin-dependent diabetes mellitus (NIDDM).

**RESEARCH DESIGN AND METHODS** — After a 6-week placebo baseline period, 102 hypertensive NIDDM patients were randomly assigned, double-blindly, to treatment with nifedipine retard (slow release) ($n$ = 52) or enalapril ($n$ = 50). The daily dosage of enalapril was increased, if required, from 10 to 20 to 40 mg and that of nifedipine from 40 to 60 to 80 mg at 4-week intervals during the 12-week titration period. Blood pressure, 24-h urinary albumin excretion (UAE), biochemical data, and serum angiotensin-converting enzyme (ACE) activity were measured at weeks −6, −4, 0, 4, 8, and 12. At week 0, venous blood was also sampled for baseline plasma atrial natriuretic peptide, renin, aldosterone, and serum insulin concentrations.

**RESULTS** — At week 12, the mean daily dose of enalapril was 35 ± 11.4 mg, and 27 (57%) patients were receiving the maximum daily dose of 40 mg. In the nifedipine group, the mean daily drug dose was 50 ± 12.9 mg, and 4 (8%) were receiving the maximum daily dose of 80 mg. Despite a dose-dependent fall in the serum ACE activity in the enalapril group, the mean arterial pressure (MAP) was reduced by only 8 mmHg throughout the 12-week titration period compared to a decline of 15, 18, and 19 mmHg at weeks 0, 4, and 12, respectively, in the nifedipine group ($P$ = 0.01 between groups). In the enalapril group, changes in MAP between weeks 0 and 12 correlated significantly with baseline plasma glucose ($r$ = 0.45, $P$ = 0.001) and aldosterone concentrations ($r$ = −0.32, $P$ = 0.02) and UAE ($r$ = 0.3, $P$ = 0.04). There was no statistically significant correlation between the changes in MAP and baseline plasma renin concentration. On multivariate analysis, the baseline renal function, glycemic control, and plasma aldosterone and serum insulin concentrations were all independently related to the changes in blood pressure in the enalapril-treated patients. No such statistical associations were observed in the nifedipine group.

**CONCLUSIONS** — In hypertensive NIDDM patients, the activity of the renin-angiotensin-aldosterone system, the level of serum insulin, glycemic control, renal function, and proteinuria may be important determinants of the blood pressure response to ACE inhibition. Good glycemic control may optimize the antihypertensive efficacy of concomitant ACE inhibitor therapy.

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Received for publication 24 October 1994 and accepted in revised form 16 February 1995.

ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ANP, atrial natriuretic peptide; CV, coefficient of variation; MAP, mean arterial pressure; NIDDM, non-insulin-dependent diabetes mellitus; RAAS, renin-angiotensin-aldosterone system; UAE, urinary albumin excretion.

Whereas angiotensin-converting enzyme inhibitors (ACEI) are generally effective and well-tolerated antihypertensive agents, variability in the therapeutic response to these agents is well-recognized (1). Factors that have been reported to determine the blood pressure responses include baseline level of blood pressure (2,3), race (4), age (5), and renal function (6,7). In addition, the efficacy of ACEIs is enhanced when the activity of the renin-angiotensin-aldosterone system (RAAS) is heightened, although ACEIs are often effective in low-renin essential hypertension (8). More recently, it has been shown that not only the antihypertensive action but also the antiproteinuric effects of ACEIs are markedly attenuated in salt-replete diabetic hypertensive rats (9), suggesting that body sodium status may influence the therapeutic efficacy of this class of drugs when diabetes coexists. Furthermore, it is well known that the antihypertensive action of ACEIs is enhanced by dietary sodium restriction and by concomitant diuretic administration (10,11). By contrast, calcium-channel–blocking agents are effective antihypertensive agents in patients with low plasma renin activity, such as the elderly and black patients, and their efficacy is little altered by concomitant diuretic therapy (12).

Disturbances of sodium and water homeostasis with reduced plasma renin and aldosterone concentrations have been reported in diabetic patients with hypertension and/or proteinuria (13–15). Apart from activity of the RAAS, few indexes have been studied as possible determinants of the antihypertensive efficacy of ACEIs and calcium-channel–blocking agents in non-insulin-dependent diabetes mellitus (NIDDM). This is important in view of the high prevalence of hypertension and its effects on the progression of complications in these patients (16). In a previously reported clinical trial comparing the long-term antihypertensive and renal effects of enalapril and nifedipine in the same cohort of patients, the majority

of the enalapril-treated patients (76%) required additional diuretic therapy to control blood pressure compared with only 14% in the nifedipine group (17). In the present report, we have examined in detail factors that correlated with the blood pressure response to these two antihypertensive agents during the 12-week period of monotherapy.

## RESEARCH DESIGN AND METHODS

— This analysis examines the relationships between blood pressure response and baseline clinical characteristics, biochemical data, and hormonal parameters in 102 Chinese NIDDM, hypertensive patients randomized to treatment with either enalapril ($n$ = 50) or nifedipine retard (slow release) ($n$ = 52) therapy. The study design and methods have been described in detail elsewhere (17), and this study concentrates on the initial 12-week dose titration period before diuretics were introduced. In brief, all of the NIDDM patients were treated with diet and/or oral hypoglycemic agents; had no significant concurrent medical history including cerebrovascular accident, ischemic heart disease, or renal failure (plasma creatinine concentration ≤200 μmol/l) at the time of recruitment; and had a mean supine blood pressure ≥150/100 mmHg at the time of randomization. The study consisted of a 6-week placebo baseline period when previous antihypertensive medications were withdrawn, and placebo tablets matched to enalapril 10 mg once daily and nifedipine retard (slow release) 20 mg twice daily were given. They were seen on three occasions (weeks −6, −4, and 0) during this placebo baseline period before being randomly assigned, in a double-blind fashion, to a 12-week active titration period when the daily dose of enalapril was increased from 10 to 20 mg and then to 40 mg and that of nifedipine was increased from 40 to 60 mg and then to 80 mg at 4-weekly intervals (weeks 4, 8, and 12) if the goal supine systolic blood pressure (≤140 mmHg) was not achieved. After the 12-week titration period, incremental diuretic therapy in the form of indapamide 2.5 mg and then frusemide 40 mg and 80 mg daily were added at 4-week intervals if the goal supine pressure was not attained (17).

At each visit during the placebo and dose titration periods, the patients reported to the hospital clinic in a fasting state, having taken their antihypertensive medication between 2 and 4 h previously. Blood pressure and pulse rate were measured after the patients had remained supine for 5 min and erect for 2 min by a single observer using a random zero sphygmomanometer. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure and was shown as a mean of supine and erect values unless otherwise stated.

At each visit in question (weeks −6, −4, 0, 4, 8, and 12), venous blood was drawn for measurements of biochemical indexes and serum angiotensin-converting enzyme (ACE) activity. At the end of the baseline period (week 0), venous blood was also drawn for measurements of plasma atrial natriuretic peptide (ANP), aldosterone, and renin and serum insulin concentrations. These were collected after the patients had remained upright for 2 min between 9 A.M. and 10 A.M. and after the measurement of blood pressure in the erect posture. Twenty-four hour urine samples were collected at each visit for measurement of albumin and creatinine to allow calculation of endogenous creatinine clearance. A midstream urine sample was also sent for culture and microscopy to exclude concomitant urinary tract infection.

Plasma ANP was measured by radioimmunoassay after extraction using Sep-Pak cartridges (Waters Chromatography Division, Millipore, Bedford, MA), as described previously (18). Intra-assay and interassay coefficients of variation (CV) were between 11 and 14% at different concentrations of ANP in human plasma. Plasma renin concentration was measured by radioimmunoassay (ERIA Diagnostics Pasteur, Marnes La Coquette, France). The interassay CV was 11% and the lowest detection limit was 7.5 ng/l. Plasma aldosterone was measured by radioimmunoassay (Diagnostic, Los Angeles, CA). The interassay CV was 12%, and the lower detection limit was 68 pmol/l. Serum ACE activity was measured by a modified spectrophotometric method (19). The intra-assay and interassay CV were both <5%. Serum insulin concentration was measured by radioimmunoassay (Pharmacia Insulin RIA 100, Pharmacia, Uppsala, Sweden). The lower detection limit was <2 μU/ml, and the intra- and interassay CVs were 6 and 13.8%, respectively.

Urinary albumin concentration was determined by immunoturbidimetry using previously published methodology (20). Intra-assay and interassay CVs were 3.3 and 6.7%, respectively, and the lower detection limit was 2.5 mg/l. Plasma and urinary electrolyte concentrations were measured by ion-selective electrodes on the parallel multichannel analyzer (American Monitor, IN). Plasma and urinary creatinine were measured by the Jaffe method on a Beckman Astra-8 Chemistry Analyzer (Beckman, Brea, CA). Plasma glucose concentration was measured by a glucose oxidase method (reagent kit, Diagnostic) and total $HbA_1$ by electrophoresis (Ciba Corning Diagnostics, Palo Alto, CA; normal range, 6.5–8.5%).

### Statistical analysis

Statistical analyses were performed using the ABstat (version 6.01, Anderson-Bell, Parker, CO) statistical package on an IBM-PC computer. The hormonal parameters and urinary albumin excretion (UAE) were positively skewed and were therefore log-transformed before analysis. The mean values of UAE during the placebo period were used as baseline values. Results are expressed as mean ± SD and geometric mean ×/÷ antilog SD as appropriate. Student's $t$ test was used to detect differences between groups. Repeated-measures analysis of variance was used to test for the effects of treatment on

**Table 1**—*Plasma hormone and enzyme levels and plasma and urinary electrolyte values at baseline (week 0)*

| | Enalapril | Nifedipine |
|---|---|---|
| *n* | 50 | 52 |
| Plasma sodium (mmol/l) | 140.3 ± 2 | 141 ± 2.1 |
| Plasma potassium (mmol/l) | 4.1 ± 0.6 | 4.0 ± 0.4 |
| 24-h urinary $Na^+$ excretion (mmol/day) | 156 ± 73 | 163 ± 69 |
| 24-h urinary $K^+$ excretion (mmol/day) | 38.2 ± 17.2 | 41.3 ± 14.9 |
| Fasting serum insulin (μU/ml) | 12.5 ×/÷ 1.7 | 12.1 ×/÷ 1.6 |
| Plasma ANP (pg/ml) | 41.8 ×/÷ 1.7 | 42.0 ×/÷ 1.6 |
| Plasma aldosterone (pmol/l) | 290 ×/÷ 1.6 | 296 ×/÷ 1.8 |
| Plasma renin (ng/l) | 26 ×/÷ 2.7 | 29.2 ×/÷ 3.1 |
| Serum ACE activity (IU/l) | 63 ×/÷ 1.7 | 65.8 ×/÷ 1.5 |

Data are means ± SD or geometric mean ×/÷ antilog SD.

blood pressure and serum ACE activity. Least-squares analysis and multiple stepwise regression analyses were used to test the associations between variables. $P < 0.05$ (two-tailed) was considered to be statistically significant.

**RESULTS**— Clinical characteristics and biochemical data at baseline have been previously reported (17). Apart from a slightly greater age ($P < 0.05$) and higher supine systolic blood pressure ($P < 0.05$) in enalapril-treated patients, the two groups were well-matched in terms of obesity, glycemic control, and renal function (17). Table 1 summarizes the baseline hormones, serum ACE activity, and electrolyte indexes in both patient groups that were similar (Table 1).

During the 12-week titration period, three patients were withdrawn from enalapril treatment because of myocardial infarction, angina, and cough in one patient each, while one patient was withdrawn from nifedipine because angina developed. In the enalapril group ($n = 47$), 36 patients (75%) required a dose increase after 4 weeks of treatment compared to 16 (31%) of the nifedipine group ($n = 51$). At week 12, 12 enalapril-treated patients (25%) were receiving daily dosages of 20 mg and 27 (57%) were receiving 40 mg. The mean daily dose of enalapril was 35 ± 11.4 mg. In the nifedipine group, 17 (33%) were receiving a daily dose of 60 mg and 4 (8%) were receiving 80 mg. The mean daily dose was 50 ± 12.9 mg.

Figure 1 summarizes changes in serum ACE activity and MAP at weeks 4, 8, and 12. With enalapril, there was a dose- and time-related reduction in serum ACE activity ($P < 0.001$ between groups). By contrast, MAP changed little with increased enalapril dose and with time (Fig. 1). With nifedipine, the reduction in MAP was consistently greater than with enalapril across the 12-week titration period ($P < 0.01$ between groups).

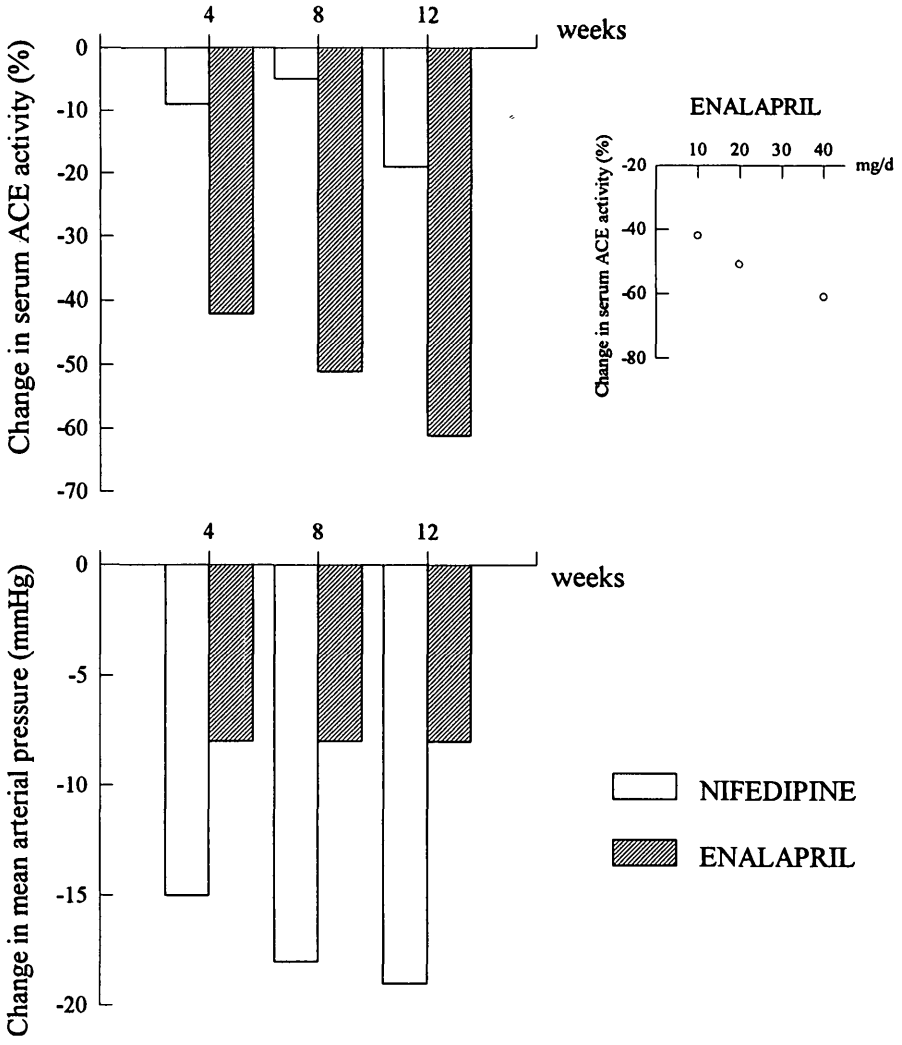


**Figure 1**—*Percentage changes in serum ACE activity and MAP compared in patients treated with enalapril and nifedipine during 12 weeks of monotherapy. Inset, relationship between the mean doses of enalapril and changes in serum ACE activity in the enalapril group during the 12 weeks of treatment.*

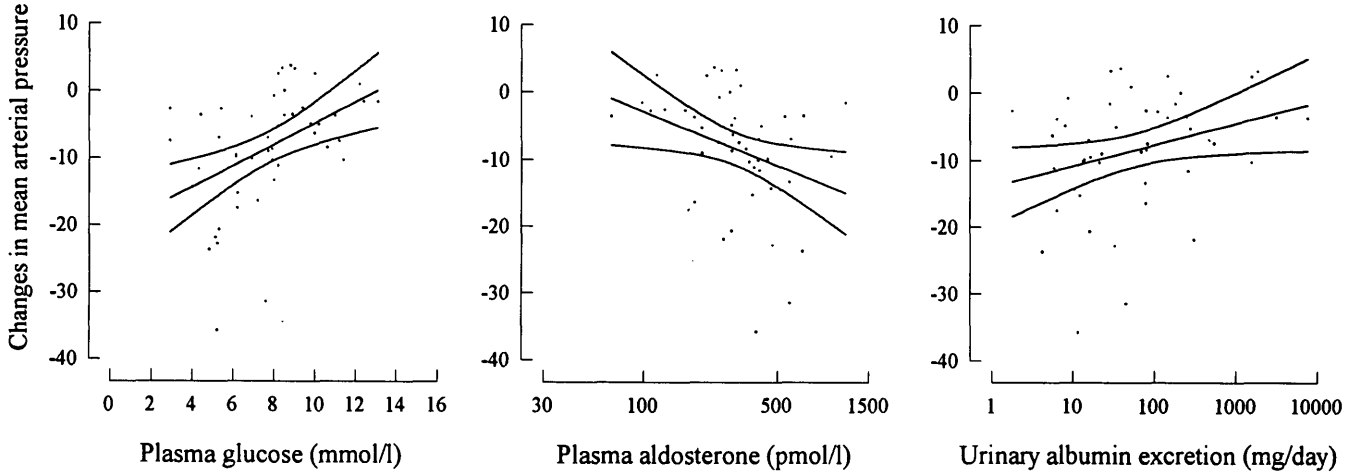


**Figure 2**—*Relationships in the enalapril-treated patients between the changes in MAP and baseline 24-h UAE (r = 0.30, P = 0.04), plasma glucose (r = 0.45, P = 0.001), and aldosterone (r = −0.33, P = 0.02) concentrations. The 24-h UAE and plasma aldosterone levels are expressed on logarithmic scales. In each case, the regression line and 95% confidence intervals are shown.*

For patients receiving enalapril, Fig. 2 summarizes relationships between baseline plasma glucose and aldosterone levels and UAE on the one hand and changes in MAP between weeks 0 and 12 on the other hand. The change in MAP correlated with baseline UAE ($r = 0.30$, $P = 0.04$) and plasma glucose ($r = 0.45$, $P = 0.001$), as well as inversely with plasma aldosterone ($r = -0.32$, $P = 0.02$) and sodium concentrations ($r = -0.31$, $P = 0.03$). There was no relationship between the changes in MAP and baseline plasma renin concentration. Table 2 summarizes relationships between baseline parameters and blood pressure response with enalapril using stepwise multiple regression, with age, body mass index, renal function, glycemic control, blood pressure, and hormonal parameters at baseline as independent variables. The baseline measures of renal function (UAE and creatinine clearance), glycemic control (fasting plasma glucose concentration and $HbA_1$), plasma aldosterone, and serum insulin concentrations were all independently related to changes in blood pressure in these patients. In contrast to results in enalapril-treated patients, there were no statistically significant relationships between any of the parameters measured at baseline and blood pressure responses in the nifedipine group.

**CONCLUSIONS** — In the treatment of hypertension, determinants of the blood pressure response to calcium-channel–blocking agents are not well-described except that they appear to be more effective in patients with low plasma renin states (12). For the responses to ACEIs, the baseline levels of blood pressure (2,3), age (5), and activity of the RAAS (1,21) have been reported as significant determinants. These two groups of antihypertensive agents are now commonly prescribed for patients with hypertension and NIDDM partly because of their beneficial or neutral effects on carbohydrate metabolism (22). However, there is little information on what determines the blood pressure response to these agents in such patients. In this respect, the antihypertensive and antiproteinuric effects of ACEIs are markedly attenuated in salt-replete diabetic, hypertensive rats, suggesting that the clinical

**Table 2**—*Standardized regression coefficients (β) of the relationships between the changes (Δ) in blood pressure parameters and baseline hormonal and biochemical indexes using multiple regression analysis in patients receiving enalapril*

| | ΔSsBP | ΔSdBP | ΔEsBP | ΔEdBP | ΔMAP |
|---|---|---|---|---|---|
| $r^2$ | 0.36 | 0.17 | 0.15 | 0.43 | 0.46 |
| *F* test | 8.5§ | 5.0‡ | 7.9‡ | 10.7§ | 9.2§ |
| Creatinine clearance (ml/min) | — | — | — | — | −0.43‡ |
| UAE (mg/day) | — | — | 0.42‡ | — | — |
| Plasma $K^+$ (mmol/l) | 0.45‡ | — | — | — | — |
| Plasma $Na^+$ (mmol/l) | −0.42‡ | — | — | — | — |
| Fasting plasma glucose (mmol/l) | 0.46§ | — | — | — | 0.38‡ |
| $HbA_1$ (%) | — | 0.32* | — | 0.33‡ | — |
| Plasma aldosterone (pmol/l) | — | −0.33† | — | −0.61§ | −0.46‡ |
| Fasting serum insulin (μU/ml) | — | — | — | 0.44‡ | 0.35‡ |

SsBP, supine systolic blood pressure; SdBP, supine diastolic blood pressure; EsBP, erect systolic blood pressure; EdBP, erect diastolic blood pressure. * $P < 0.05$; † $P < 0.02$; ‡ $P < 0.01$; § $P < 0.001$.

efficacy of this class of drugs may be limited in salt-replete states (9).

Several mechanisms may contribute to sodium retention in diabetes. Glomerular hyperfiltration of glucose due to hyperglycemia can stimulate the proximal tubular glucose-sodium cotransporter, resulting in sodium retention, although marked hyperglycemia may reverse this tendency due to osmotic diuresis and hypovolemia (23,24). Insulin may enhance sodium reabsorption through stimulation of the renal tubular sodium pump and the sodium-hydrogen countertransporter and by amplifying the action of aldosterone on sodium and potassium transport (25,26). Renal failure as a late complication can further promote sodium and fluid retention in diabetic patients (27); apart from reduced glomerular filtration, the exact mechanism underlying this salt retention remains uncertain. We have previously reported that in hypertensive NIDDM patients, proteinuria was associated with increased plasma ANP and reduced urinary dopamine output, suggesting the possibility of defective natriuretic mechanisms (14).

In the present study, we observed that the antihypertensive effect of the ACEI enalapril was greatest in patients with the least abnormalities in glucose homeostasis (as determined by plasma glucose, $HbA_1$, and insulin concentrations) and renal function (measured as endogenous creatinine clearance and UAE) and the highest concentration of plasma aldosterone. From the opposite viewpoint, patients with the least satisfactory glycemic control, the most impaired renal function, and the lowest circulating concentrations of aldosterone showed little response in arterial pressure to the ACEI. Although formal assessments of body sodium content and plasma volume were not carried out in the present study, we conclude that patients who showed a poor response to enalapril were likely to be relatively volume-expanded, perhaps as a result of unsatisfactory control of diabetes and reduced renal function. Under these circumstances, reduced plasma renin and aldosterone concentrations as well as minimal blood pressure responses to ACE inhibition would be predictable. Such patients seemingly require restriction of dietary intake, the addition of diuretic therapy (17), or perhaps the combination of an ACEI and calcium-channel–blocking agents.

By contrast, no clear determinants of the blood pressure response to calcium-channel–blocking agents were identified. Increased peripheral vascular resistance due to enhanced vasoconstriction appears to be an essential feature of hypertension in NIDDM (16). Calcium ions, which may be of extra- or intracellular origin, bind to calmodulin, resulting in the phosphorylation of myosin, which is an essential step in the contraction of vascular smooth muscle cells (29). Although the intracellular cation metabolism in diabetes is still unclear, hypertensive NIDDM patients have been reported to show increased intracellular calcium concentration (30), which might promote vasoconstriction. Calcium-channel–blocking agents such as nifedipine have been shown to lower blood pressure by direct arteriolar and venous vasodilation (31). In view of these direct actions of calcium-channel–blocking agents on the vasculature, the lack of association between clinical efficacy and any of the baseline parameters measured in the current study is not surprising.

Although our data are derived specifically from Chinese patients with hypertension and NIDDM and therefore may not be extrapolated to other racial groups, it is noteworthy that ACEIs are effective in Chinese patients with essential hypertension (32,33). At least in Chinese patients, therefore, one can expect greater antihypertensive effects with ACEIs in those with preserved renal function, good glycemic control, and no suppression of the RAAS. From the practical viewpoint, it is important to try for good glycemic control in order to maximize the antihypertensive efficacy of concomitant ACEI therapy.

**Acknowledgments**— The study was wholly sponsored by Merck, Sharp and Dohme.

We thank Margaret Cheung and Angela Wong, our research nurses, for dedicated work and Stanley Ho for performing the insulin assay.

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