2000

The Long Term Effects of Angiotensin Converting Enzyme Inhibition and Metabolic Control on Cardiovascular and Renal Outcomes in Hypertensive Type 2 Diabetic Patients

Julien C. N. CHAN
Chinese University of Hong Kong

Gary T. C. KO
Chinese University of Hong Kong

Denis H. Y. Leung
Singapore Management University, denisleung@smu.edu.sg

DOI: https://doi.org/10.1046/j.1523-1755.2000.00879.x

Kidney International, Vol. 57 (2000), pp. 590–600

Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients

JULIANA C.N. CHAN, GARY T.C. KO, DENIS H.Y. LEUNG, ROBERT C.K. CHEUNG, MARGARET Y.F. CHEUNG, WING-YEE SO, RAMASMYIYER SWAMINATHAN, M. GARY NICHOLLS, JULIAN A.J.H. CRITCHLEY, and CLIVE S. COCKRAM

Department of Medicine and Therapeutics, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong

Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients.

Background. In hypertensive type 2 diabetic patients, treatment with angiotensin-converting enzyme (ACE) inhibitors is associated with a lower incidence of cardiovascular events than those treated with calcium channel-blocking agents. However, the long-term renal effects of ACE inhibitors in these patients remain inconclusive. In 1989, we commenced a placebo-controlled, double-blind, randomized study to examine the antialbuminuric effects of enalapril versus nifedipine (slow release) in 102 hypertensive, type 2 diabetic patients. These patients have been followed up for a mean trial duration of 5.5 ± 2.2 years. We examined the determinants, including the effect of ACE inhibition on clinical outcomes in these patients.

Methods. After a six-week placebo-controlled, run-in period, 52 patients were randomized double-blind to receive nifedipine (slow release) and 50 patients to receive enalapril. After the one-year analysis, which confirmed the superior antialbuminuric effects of enalapril (−54%) over nifedipine (+11%), all patients were continued on their previously assigned treatment with informed consent. They were subdivided into normoalbuminuric ($N = 43$), microalbuminuric ($N = 34$), and macroalbuminuric ($N = 25$) groups based on two of three 24-hour urinary albumin excretion (UAE) measurements during the run-in period. Renal function was shown by the 24-hour UAE, creatinine clearance (C_{Cr}), and the regression coefficient of the yearly plasma creatinine reciprocal (β-1/Cr). Clinical endpoints were defined as death, cardiovascular events, and/or renal events (need for renal replacement therapy or doubling of baseline plasma creatinine).

Results. In the whole group, patients treated with enalapril were more likely to revert to being normoalbuminuric (23.8 vs. 15.4%), and fewer of them developed macroalbuminuria (19.1 vs. 30.8%) compared with the nifedipine-treated patients ($P < 0.05$). In the microalbuminuric group, treatment with enalapril ($N = 21$) was associated with a 13.0% ($P < 0.01$) reduction in 24-hour UAE compared with a 17.3% increase in the nifedipine group ($N = 13$). In the macroalbuminuric patients, enalapril treatment ($N = 11$) was associated with stabilization compared with a decline in renal function in the nifedipine group, as shown by the β-1/Cr (0.65 ± 4.29 vs. -1.93 ± 2.35 $1/\mu mol \times 10^{-3}$, $P < 0.05$) after adjustment for baseline values. Compared with the normoalbuminuric and microalbuminuric patients, those with macroalbuminuria had the lowest mean C_{Cr} (75.5 ± 24.1 vs. 63.5 ± 21.3 vs. 41.9 ± 18.5 mL/min, $P < 0.001$) and the highest frequency of clinical events (4.7 vs. 5.9 vs. 52%, $P < 0.001$). On multivariate analysis, β-1/Cr ($R^2 = 0.195$, $P < 0.001$) was independently associated with baseline HbA_{1c} ($\beta = -0.285$, $P = 0.004$), whereas clinical outcomes ($R^2 = 0.176$, $P < 0.001$) were independently related to the mean low-density lipoprotein cholesterol ($\beta = 2.426$, $P = 0.018$), high-density lipoprotein cholesterol ($\beta = -8.797$, $P = 0.03$), baseline UAE ($\beta = 0.002$, $P = 0.04$), and mean C_{Cr} during treatment ($\beta = -0.211$, $P = 0.006$).

Conclusion. In this prospective cohort analysis involving 102 hypertensive, type 2 diabetic patients with varying degrees of albuminuria followed up for a mean duration of five years, we observed the importance of good metabolic and blood pressure control on the progression of albuminuria and renal function. Treatment with enalapril was associated with a greater reduction in albuminuria than with nifedipine in the entire patient group, and especially in those with microalbuminuria. In the macroalbuminuric patients, the rate of deterioration in renal function was also attenuated by treatment with enalapril.

The coexistence of hypertension in diabetic patients markedly increases cardiovascular risks and the rate of deterioration of renal function [1, 2]. On the other hand, optimal control of blood pressure (BP) and metabolic parameters has been shown to reduce cardiovascular and renal deaths [2–7]. Angiotensin II has major effects on renal hemodynamics and cellular growth [8]. Treatment with angiotensin-converting enzyme (ACE) inhibitors is associated with a reduction of proteinuria in both type 1 and type 2 diabetic patients, an effect independent of the degree of BP reduction [9]. This class of drug has also been shown to reduce the rate of deterioration of renal function in both type 1 [10] and normotensive type

Key words: renal hemodynamics, cardiovascular disease, blood pressure, albuminuria, enalapril, nifedipine.

Received for publication December 17, 1998
and in revised form July 27, 1999
Accepted for publication August 13, 1999

2 diabetic patients [11, 12]. However, in hypertensive type 2 diabetic patients, the possible beneficial effects of ACE inhibitors over other antihypertensive drugs remain controversial.

In the few long-term studies, lasting one year or more, that aimed to examine the renal effects of ACE inhibitors in hypertensive type 2 diabetic patients, ACE inhibitor treatment had similar effects on the progression of renal function as other antihypertensive drugs, including calcium channel-blocking agents [13–15]. In the United Kingdom Prospective Diabetes Study (UKPDS), intensive control of BP was associated with reduced mortality [16], which was not different between patients treated with captopril or atenolol [17]. On the other hand, two other studies have confirmed a lower incidence of cardiovascular events in patients treated with ACE inhibitors (enalapril or fosinopril) than those treated with calcium channel-blocking agents (nisoldipine or amlodipine) in hypertensive type 2 diabetic patients [18, 19]. In these two relatively short-term studies, the renal effects of the ACE inhibitors in these patients were inconclusive.

In 1989, we commenced a randomized, double-blind, placebo-controlled study to examine the effects of enalapril versus nifedipine (slow release) on urinary albumin excretion (UAE) in 102 hypertensive type 2 diabetic patients with preserved renal function. At one year, we reported the superior antiproteinuric effect of enalapril over nifedipine in these patients, despite similar BP control [14]. These patients have since been followed up at three-month intervals while receiving their previously assigned treatment for a mean total duration of 5.5 years. To test the hypothesis that for similar control of BP, treatment with enalapril was associated with superior renoprotective effects compared with those with nifedipine, we performed a prospective cohort analysis to examine the determinants of renal function and clinical outcomes in these patients.

METHODS

The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong, and its design has been previously described in detail [14]. It was a randomized, double-blind, placebo-controlled study examining the effects of enalapril and nifedipine (slow release) on UAE in hypertensive type 2 diabetic patients. Inclusion criteria included a diagnosis of type 2 diabetes, as defined by the World Health Organization [20], and no history of ketosis. All patients were treated with diet or oral agents, and none were receiving insulin treatment or lipid-lowering drugs at the time of recruitment. None of the patients had a significant past medical history of cardiovascular disease, including cerebrovascular accident, myocardial infarction, or unstable angina, or renal impairment, as defined by a plasma creatinine of greater than 200 μmol/L. All patients gave written informed consent and underwent history taking and physical examination.

Patients fulfilling the inclusion criteria who had a supine BP $\geq$ 150/95 mm Hg or were established on antihypertensive drugs entered a six-week placebo-controlled, run-in period, after withdrawal of all antihypertensive drug therapy, if any. BP was measured after five minutes of lying (supine) and two minutes of standing (erect), with two readings in each position at one minute apart. The mean arterial pressure (MAP) was defined as diastolic BP plus one third of the difference between systolic and diastolic BP, and the mean of the supine and erect BP values was used. During the six-week run-in period, fasting blood was sampled for routine biochemistry, and 24-hour urinary collections were made on three occasions for measurement of endogenous creatinine clearance (C_{Cr}) and UAE. All patients received placebo tablets matching for enalapril 10 mg daily and nifedipine (slow release) 20 mg twice daily.

At the end of the six-week run-in period, patients with a mean supine systolic BP between 150 and 220 mm Hg and/or diastolic BP $\geq$ 100 mm Hg were randomized in a double-blind fashion to receive active treatment with either enalapril 10 mg once daily or nifedipine (slow release) 20 mg twice daily with matching placebo tablets for the alternative drug. A schedule of 102 allocation numbers corresponding to similarly numbered drug supplies was provided for this purpose. Patients with microalbuminuria or macroalbuminuria were assigned an allocation number in a descending manner, whereas those with normoalbuminuria were assigned an allocation number in an ascending manner. The dosage was increased at four-week intervals during a 12-week titration period to achieve a target supine systolic BP $<$ 140 mm Hg at two- to four-hours postdose. Enalapril was increased stepwise from 10 mg daily to a maximum of 40 mg daily. Nifedipine (slow release) was increased from 20 mg twice daily (40 mg per day) stepwise to a maximum of 40 mg twice daily (80 mg per day). Following the 12-week titration period, indapamide, a thiazide-like diuretic, in a dosage of 2.5 mg daily, was added, followed by replacement with frusemide at 40 to 80 mg daily, if the target BP was not achieved. All patients returned at three-month intervals for the examination of body weight and BP and measurement of routine biochemistry, including 24-hour urinary collections. At one year, the majority (86%) of the nifedipine-treated patients had achieved their target BP with a median daily dosage of 60 mg. By contrast, 76% of the enalapril-treated patients required additional diuretic treatment compared with 14% in the nifedipine group [14].

After the one-year analysis, all patients were continued on their previously assigned treatment with informed consent. Because of the worsening of metabolic control

in the diuretic-treated patients, diuretics were withdrawn from all patients if possible. Additional antihypertensive drugs were used to optimize control of BP with the exception of use of ACE inhibitors in the nifedipine group. These patients continued to be followed up at three-month intervals, with documentation of all clinical and biochemical parameters. Drug compliance was repeatedly reinforced by the research nurse and was confirmed by tablet counting. Patients were considered to be compliant if 80% or more of medications were taken.

Laboratory assays

The laboratory assays have been described [14]. Plasma glucose was measured by a glucose oxidase method (Diagnostic Chemicals Ltd., Prince Edward Island, Canada). The intra-assay coefficient of variation (CV) of glucose was 2% at 6.6 mmol/L. HbA_{1c} was measured by an automated ion-exchange chromatographic method (Bio-Rad Laboratory, Hercules, CA, USA). Interassay and intra-assay CV for HbA_{1c} was $\leq$3.1% at values below 6.5%. Total cholesterol (TC) and triglyceride (TG) were assayed enzymatically with commercial reagents (Baker Instruments Corporation, Allentown, PA, USA) on a Cobas Mira analyzer (Hoffman-La Roche and Co., Basle, Switzerland). High-density lipoprotein cholesterol (HDL-C) was determined after fractional precipitation with dextran sulfate-$MgCl_2$. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald's formula [21]. Apolipoproteins A-I (apo A) and apo B were assayed by radioimmunoassays (Array analyzer and reagents; Beckman Instruments Inc., Bera, CA, USA). Interassay CVs were 1.9% for TC, 1.9% for TG, 5.4% for HDL-C, 2.2% for apo A-I, and 2.8% for apo B. Plasma and urinary creatinine concentrations were measured on a multichannel analyzer (Parallel American Monitor, IN, USA). Urinary albumin was measured by immunoturbidimetry with intra-assay and interassay CVs of 3.3 and 6.7%, respectively. The lowest detection limit was 2.5 mg/L [22].

Statistical analysis

The primary end point of the one-year analysis was a reduction in 24-hour UAE. The study was designed to give a 90% power at 5% level to show that one drug was at least two times as effective as the other in reducing UAE [14]. In the subsequent prospective cohort analysis, we examined the effects of BP, metabolic indices, and assigned treatment on renal parameters. Patients were divided into normoalbuminuric, microalbuminuric, and macroalbuminuric groups based on two of three 24-hour UAE measurements during the initial six-week run-in period [23]. The mean values of all three measurements were taken as the baseline values. The rate of deterioration of renal function was shown by the regression coefficient (β) of the yearly plasma creatinine reciprocal (1/Cr) and the percentage of yearly change in 24-hour C_{Cr}. All of the three-month 24-hour UAE measurements were used to calculate the percentage yearly change in UAE during the treatment period. All measurements of UAE, BP, fasting plasma glucose, HbA_{1c}, TC, LDL-C, HDL-C, and triglyceride were used to calculate the mean values during the treatment period. UAE was logarithmically transformed because of its skewed distribution.

All data are shown as mean $\pm$ SD or geometric mean $\times/\div$ antilog SD as appropriate. Associations between variables were examined using partial correlation coefficients after adjustments for age and gender. Analysis of covariance (ANCOVA), Student's *t*-test, paired *t*-test, chi-square test, and repeated-measures analysis of variance (ANOVA) were used for between-group comparisons with adjustment for baseline values, as appropriate. Stepwise regression analysis was used to determine the independent predictors for renal parameters and clinical endpoints. The latter was defined as death, cardiovascular (including stroke, myocardial infarction, heart failure requiring hospitalization, revascularization procedures) and/or renal events (need for renal replacement therapy or doubling of baseline plasma creatinine). The Kaplan–Meier survival analysis was used to examine the effects of albuminuric states on clinical endpoints. A P value < 0.05 was considered to be significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS version 6.0).

RESULTS

Table 1 summarizes the baseline clinical and biochemical characteristics of the 102 hypertensive type 2 diabetic patients in 1989 [14]. Despite randomization, patients assigned to receive enalapril treatment had a higher mean age (by 4 years), serum TC, LDL-C, and apo B than the nifedipine group at baseline. At one year, patients treated with enalapril had a 54% reduction in 24-hour UAE compared with an 11% increase in the nifedipine-treated group [14]. These patients were subsequently followed up for a mean period of 5.5 $\pm$ 2.2 years.

Table 1 also summarizes the mean values of all clinical and biochemical parameters during the five-year treatment period among patients treated with either enalapril or nifedipine. The mean systolic BP and HbA_{1c} were higher during treatment with enalapril compared with nifedipine. Comparing baseline and mean values during treatment, plasma creatinine increased and C_{Cr} decreased in both groups, whereas 24-hour UAE significantly increased in the nifedipine group but remained unchanged in the enalapril group.

By the end of the five-year study period four patients had died, mainly because of cardiovascular events, and with similar rates between the two treatment groups. Eleven patients had renal events, six in the enalapril

Table 1. Clinical and biochemical characteristics of the 102 hypertensive, type 2 diabetic patients at baseline and during five-year treatment with either enalapril or nifedipine

Variables	Total patients ($N = 102$)	Enalapril group ($N = 50$)	Nifedipine group ($N = 52$)	P value
Age *years*	58.0 ± 9.8	60.0 ± 9.3	56.2 ± 9.9	0.047
Body mass index kg/m^2	24.9 ± 3.0	25.1 ± 2.9	24.8 ± 3.0	0.521
Follow-up period *years*	5.5 ± 2.2	5.2 ± 2.4	5.8 ± 1.9	0.165
Systolic blood pressure *mm Hg*	169.2 ± 15.2	172.1 ± 16.5	166.5 ± 13.4	0.062
	134.4 ± 10.8	137.0 ± 11.8[d]	132.2 ± 9.4[d]	0.032
Diastolic blood pressure *mm Hg*	92.5 ± 10.9	92.5 ± 12.4	92.5 ± 9.5	0.980
	72.4 ± 11.4	72.1 ± 14.6[e]	72.6 ± 7.8[e]	0.823
Mean arterial pressure *mm Hg*	118.1 ± 9.6	119.0 ± 10.9	117.2 ± 8.0	0.336
	93.6 ± 6.9	94.9 ± 7.8[e]	92.5 ± 5.9[e]	0.102
Fasting plasma glucose *mmol/L*	8.3 ± 2.2	8.4 ± 2.3	8.2 ± 2.1	0.651
	8.0 ± 1.7	7.8 ± 1.9	8.2 ± 1.4	0.205
HbA_{1c} %	7.50 ± 1.15	7.70 ± 1.17	7.32 ± 1.11	0.090
	7.30 ± 0.89	7.58 ± 0.82	7.06 ± 0.88[c]	0.004
Total cholesterol *mmol/L*	5.71 ± 1.15	5.97 ± 1.34	5.45 ± 0.87	0.024
	5.59 ± 0.91	5.66 ± 0.91	5.54 ± 0.92	0.544
Triglyceride *mmol/L*	1.99 ± 1.41	1.93 ± 1.38	2.04 ± 1.46	0.708
	2.03 ± 1.27	2.08 ± 1.27	1.98 ± 1.28	0.720
HDL-C *mmol/L*	1.17 ± 0.31	1.18 ± 0.30	1.17 ± 0.33	0.782
	1.26 ± 0.29	1.23 ± 0.29	1.28 ± 0.29[d]	0.469
LDL-C *mmol/L*	3.62 ± 1.11	3.91 ± 1.25	3.34 ± 0.89	0.010
	3.43 ± 0.72	3.51 ± 0.71[c]	3.36 ± 0.73	0.292
Apolipoprotein A *mg/dL*	124.6 ± 25.9	125.1 ± 24.1	124.1 ± 27.6	0.847
Apolipoprotein B *mg/dL*	99.8 ± 23.2	106.6 ± 27.3	93.4 ± 16.4	0.004
Plasma creatinine *μmol/L*	85.3 ± 25.8	85.4 ± 23.8	85.1 ± 27.8	0.950
	101.1 ± 39.7	103.5 ± 30.0[e]	99.0 ± 46.8[e]	0.589
Creatinine clearance *mL/min*	75.4 ± 26.7	73.7 ± 25.8	76.9 ± 27.6	0.542
	63.5 ± 25.5	61.5 ± 22.9[e]	65.3 ± 27.7[d]	0.461
24-hour UAE[a] *mg/day*	75.9 ×/÷ 6.7	73.4 ×/÷ 6.9	78.5 ×/÷ 6.6	0.859
	89.4 ×/÷ 6.7	78.8 ×/÷ 6.5	100.6 ×/÷ 7.0[c]	0.524
β-1/Cr	−0.35 ± 2.83	−0.18 ± 3.75	−0.51 ± 1.53	0.563

For variables with 2 sets of values, the upper line shows the baseline values and the lower line shows the mean values during the treatment period.

[a] Data are mean ×/÷ antilog SD

[b] P value comparing enalapril and nifedipine group

[c] $P < 0.05$

[d] $P < 0.01$

[e] $P < 0.001$ comparing baseline values and mean values within each treatment group (serum apo A and apo B were measured only at baseline)

Abbreviations are: HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; UAE, urinary albumin excretion; β-1/Cr, regression coefficient of yearly plasma creatinine reciprocal.

group and five in the nifedipine group. Over 20% of patients required lipid-lowering drugs (enalapril group, 22%, $N = 11$; nifedipine group, 25%, $N = 13$, P = NS), and 12% were treated with insulin (enalapril group, 8%, $N = 4$; nifedipine group, 15%, $N = 8$, P = NS). The use of these drugs was similar between both treatment groups. The majority of the enalapril-treated patients (68%, $N = 34$) required additional antihypertensive drugs for the control of BP compared with 46% ($N = 24$, $P < 0.05$) in the nifedipine group. Except for the initial 12-month study period (enalapril group, 76%; nifedipine group, 14%), the use of diuretics was similar between the two groups (enalapril group, 12%, $N = 6$; nifedipine group, 17%, $N = 9$, P = NS) after the one-year analysis. Because of the protocol, none of the nifedipine-treated patients received ACE inhibitor therapy during the five-year follow-up period.

Table 2 shows the changes in albuminuric status in these patients divided according to their assigned treatments and baseline albuminuric groups. In the normoalbuminuric group, there is no subsequent change in UAE with either treatment. In the microalbuminuric group, treatment with enalapril was associated with a 13.0% reduction in 24-hour UAE compared with baseline (from 87.9 ×/÷ 1.2 mg/day to 76.7 ×/÷ 3.2 mg/day, $P < 0.01$). This was in contrast to a 17.3% increase in the nifedipine group (from 82 ×/÷ 2 mg/day to 97 ×/÷ 3.1 mg/day, P = NS). Less enalapril-treated microalbuminuric patients progressed to develop macroalbuminuria, and more patients reverted to become normoalbuminuria (Table 2). In the macroalbuminuric group, there was a trend for 24-hour UAE to decline after treatment with either enalapril or nifedipine, but the changes within or between groups were not significant. When patients with macroalbuminuria or microalbuminuria were combined for analysis, no significant changes in the 24-hour UAE during treatment were detected between these two treatment groups. When all patients were included in the analysis, more enalapril-treated patients reverted to become normoalbuminuric (23.8 vs. 15.4%), and fewer of them de-

Table 2. Progression of albuminuria in patients treated with enalapril or nifedipine based on their albuminuric state at baseline

Baseline	End of study	Treatment		*P* value
		Enalapril	Nifedipine	
Normoalbuminuria ($N = 43$)				0.45
	Normo-	14 (77.8%)	18 (72%)	
	Micro-	4 (22.2%)	5 (20%)	
	Macro-	0	2 (8%)	
Microalbuminuria ($N = 34$)				0.046
	Normo-	5 (23.8%)	2 (15.4%)	
	Micro-	12 (57.1%)	7 (53.8%)	
	Macro-	4 (19.1%)	4 (30.8%)	
Macroalbuminuria ($N = 25$)				0.086
	Normo-	0	0	
	Micro-	1 (9.1%)	3 (21.4%)	
	Macro-	10 (90.9%)	11 (78.6%)	

Definition of albuminuria was based on two of three 24-hour urinary albumin excretions.

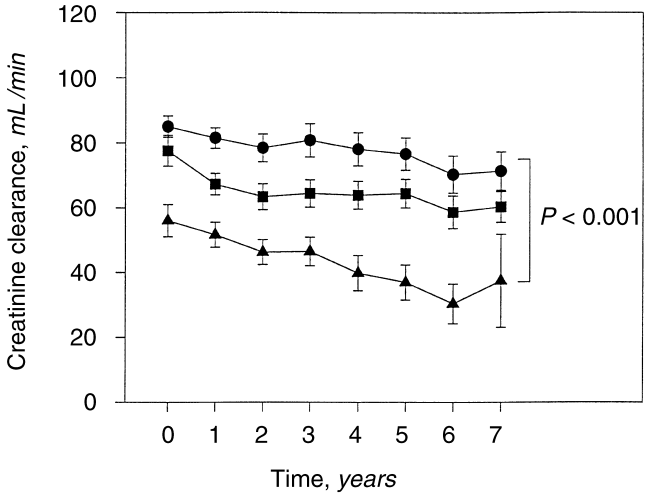

Fig. 1. Rates of deterioration of renal function, expressed as 24-hour creatinine clearance, in hypertensive type 2 diabetic patients, subdivided into normoalbuminuric (●), microalbuminuric (■), and macroalbuminuric (▲) groups based on two of three 24-hour urinary albumin excretion measurements at baseline.

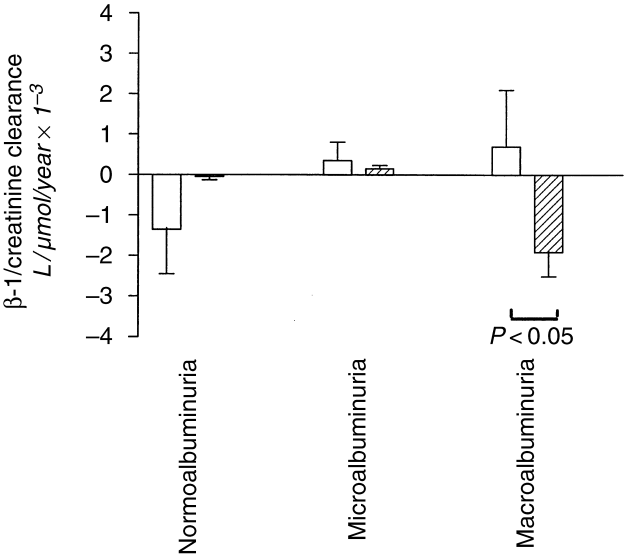

Fig. 2. Effects of enalapril (□) and nifedipine (▨) treatment on progression of renal function, expressed as regression coefficient of yearly plasma creatinine reciprocal (β-1/Cr) in hypertensive type 2 diabetic patients subdivided into normoalbuminuric, microalbuminuric, and macroalbuminuric groups based on two of three 24-hour urinary albumin excretion measurements at baseline.

veloped macroalbuminuria (19.1 vs. 30.8%) compared with the nifedipine-treated patients ($P < 0.05$).

The clinical and biochemical characteristics of patients subdivided according to their baseline albuminuric status were analyzed. Increasing albuminuria was associated with higher BP, worse metabolic indices, and renal function, both at baseline and during the treatment period (data not shown). The C_{Cr} in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria were 84.9 ± 21.3, 77.5 ± 27.3, and 56.0 ± 24.8 mL/min ($P < 0.001$) at baseline, and their mean values during treatment were 75.5 ± 24.1, 63.5 ± 21.3, and 41.9 ± 18.5 mL/min ($P < 0.001$), respectively. The average rates of fall of C_{Cr} in patients with normoalbuminuria, microalbuminuria, and macroalbuminuria were, respectively, −2.7 ± 4.2 mL/min/year (range −16.3, 7.9; median − 2.7 mL/min/year), −2.9 ± 4.9 mL/min/year (range −24.5, 7.3; median −2.6 mL/min/year), and −2.5 ± 9.0 mL/min/year (range −20.7, 21.9; median −3.8 mL/min/year, $P = 0.971$). Figure 1 shows the progression of renal function, expressed as C_{Cr}, in these three groups of patients, irrespective of their duration of follow-up. Using repeated-measures ANOVA, macroalbuminuric patients had a faster rate of decline in renal function than the other two groups.

Figure 2 shows the effects of nifedipine and enalapril on the progression of renal function, as shown by the regression coefficients of yearly plasma creatinine reciprocal (β-1/Cr). In the macroalbuminuric group, enalapril treatment was associated with stabilization compared

Table 3. Age and sex adjusted partial correlation coefficients between renal parameters and different variables at baseline and during treatment in hypertensive type 2 diabetic patients

	β-1/Cr		Mean creatinine clearance during treatment		Mean 24-hour UAE during treatment		Percentage change per year in C_{Cr}		Percentage change per year in UAE	
Variables	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
BMI	0.071	0.516	0.278	0.010	−0.046	0.678	0.072	0.674	−0.012	0.943
Systolic BP	−0.057	0.606	−0.163	0.137	−0.020	0.856	0.081	0.634	0.159	0.348
Diastolic BP	0.102	0.351	0.223	0.041	−0.241	0.026	0.134	0.429	0.054	0.752
Fasting PG	−0.215	0.048	−0.268	0.013	0.378	<0.001	0.039	0.819	−0.245	0.144
HbA_{1c}	−0.307	0.004	−0.222	0.041	0.279	0.010	0.122	0.472	−0.065	0.701
TC	−0.106	0.335	−0.147	0.179	0.485	<0.001	0.034	0.842	−0.077	0.652
Triglyceride	−0.210	0.053	−0.081	0.464	0.326	0.002	0.227	0.177	0.054	0.750
HDL-C	0.131	0.234	−0.170	0.120	0.158	0.148	0.167	0.323	−0.179	0.289
LDL-C	−0.018	0.869	−0.050	0.650	0.244	0.025	−0.170	0.319	−0.036	0.834
Apo A	0.116	0.289	−0.183	0.093	0.133	0.225	0.088	0.606	−0.203	0.227
Apo B	−0.198	0.070	−0.096	0.383	0.430	<0.001	−0.070	0.682	0.054	0.751
Plasma creatinine	−0.084	0.432	−0.450	<0.001	0.324	0.002	0.447	0.006	−0.216	0.200
C_{Cr}	0.208	0.057	0.717	<0.001	−0.319	0.003	−0.133	0.433	−0.136	0.421
24-hour UAE	−0.235	0.030	−0.393	<0.001	0.710	<0.001	−0.225	0.181	−0.160	0.344
Mean values during treatment										
Systolic BP	−0.391	<0.001	−0.319	0.003	0.330	0.002	−0.120	0.484	0.192	0.256
Diastolic BP	−0.089	0.419	0.138	0.209	−0.097	0.378	−0.014	0.935	0.180	0.288
Fasting PG	−0.132	0.228	−0.039	0.726	−0.039	0.723	−0.514	0.001	0.084	0.621
HbA_{1c}	−0.156	0.154	−0.207	0.057	0.121	0.269	−0.300	0.071	0.218	0.195
TC	−0.039	0.724	−0.127	0.247	0.429	<0.001	−0.219	0.180	0.132	0.422
Triglyceride	−0.183	0.094	−0.203	0.063	0.257	0.018	−0.146	0.377	0.394	0.013
HDL-C	0.243	0.025	−0.030	0.788	−0.002	0.983	−0.003	0.988	−0.332	0.039
LDL-C	−0.048	0.660	0.031	0.788	−0.002	0.983	−0.115	0.485	0.194	0.236
Plasma creatinine	−0.386	<0.001	0.031	0.778	0.263	0.015	0.057	0.730	0.323	0.045
β-1/Cr	—	—	0.295	0.006	−0.321	0.003	0.267	0.091	0.021	0.897
C_{Cr}	0.295	0.006	—	—	−0.377	<0.001	0.345	0.031	−0.344	0.032
24-hour UAE	−0.321	0.003	−0.377	<0.001	—	—	−0.353	0.027	0.594	<0.001
Percentage change per year in C_{Cr}	0.267	0.091	0.345	0.031	−0.353	0.027	—	—	−0.523	0.001
Percentage change per year in UAE	0.021	0.897	−0.344	0.032	0.594	<0.001	−0.523	0.001	—	—

Abbreviations are: BMI, body mass index; BP, blood pressure; PG, plasma glucose; HbA_{1c}, glycated hemoglobin; TC, total cholesterol; HDL-C and LDL-C, high and low density lipoprotein cholesterol; Apo A and Apo B, apolipoprotein A and B; C_{Cr}, creatinine clearance; UAE, urinary albumin excretion; β-1/Cr, regression coefficient of yearly plasma creatinine reciprocal.

with a decline in renal function in the nifedipine group ($P < 0.05$), after adjustment for baseline values. When patients with microalbuminuria or macroalbuminuria were combined for analysis, renal function also tended to stabilize in the enalapril group compared with a decline in the nifedipine group, although this did not reach statistical significance (β-1/Cr: 0.46 ± 2.94 L/μmol/year $\times 10^{-3}$ vs. -0.93 ± 2.01 L/μmol/year $\times 10^{-3}$, P = NS).

Table 3 summarizes the age- and sex-adjusted partial correlation coefficients between renal parameters and different variables at baseline and during treatment. Renal function, as indicated by β-1/cr, mean 24-hour UAE and C_{Cr} during treatment and yearly percentage changes in C_{Cr} and UAE, were closely associated with BP, glycemic, and lipid indices at baseline and during treatment. Table 4 summarizes the results of the stepwise regression analysis examining the effects of these variables, including age, duration of disease, metabolic control, BP, and assigned treatment with either enalapril (1) or nifedipine (0) on renal parameters and clinical outcomes. Twenty-four–hour UAE during treatment was independently associated with UAE, fasting plasma glucose, serum apo A at baseline, and plasma creatinine and C_{Cr} during treatment. The mean C_{Cr} during treatment was determined by age, male gender, fasting plasma glucose, UAE, and C_{Cr} at baseline. The rate of change of plasma creatinine reciprocal (β-1/Cr) was independently associated, with a mean C_{Cr} during treatment and baseline HbA_{1c}. The clinical outcomes (death, cardiovascular events, or renal events) were independently related to mean LDL-C and HDL-C, baseline UAE, and mean C_{Cr} during treatment.

DISCUSSION

Renal failure is a leading cause of early mortality and morbidity in diabetic patients. Type 2 diabetes is the

Table 4. Multiple regression analysis (stepwise forward) examining the effects of age, sex, duration of follow-up, metabolic control (fasting plasma glucose, HbA_{1c}, lipid parameters, plasma creatinine concentration, 24-hour UAE and creatinine clearance), blood pressure and assigned treatment with either enalapril (1) or nifedipine (0) on renal parameters and clinical outcomes

	β	*P* value
β-1/Cr ($R^2 = 0.195$, $F = 11.93$, $P < 0.001$)		
Mean plasma creatinine concentration during treatment	−0.310	0.002
Baseline HbA_{1c}	−0.285	0.004
Mean creatinine clearance during treatment ($R^2 = 0.715$, $F = 46.73$, $P < 0.001$)		
Age	−0.262	<0.001
Baseline creatinine clearance	0.613	<0.001
Baseline 24-hour UAE	−0.194	0.001
Baseline fasting plasma glucose	−0.120	0.042
Male sex	−0.114	0.049
Mean 24-hour UAE during treatment ($R^2 = 0.699$, $F = 34.99$, $P < 0.001$)		
Baseline 24-hour UAE	0.511	<0.001
Mean creatinine clearance during treatment	0.399	<0.001
Mean plasma creatinine concentration during treatment	0.359	<0.001
Baseline creatinine clearance	0.291	0.005
Baseline apolipoprotein A	0.172	0.007
Baseline fasting plasma glucose	0.160	0.013
Percentage change per year in UAE ($R^2 = 0.516$, $F = 30.59$, $P < 0.001$)		
Baseline 24-hour UAE	1.444	<0.001
Mean 24-hour UAE during treatment	−1.409	<0.001
Baseline LDL-C	0.171	0.025
Clinical outcomes (death, cardiovascular events, and renal events) ($R^2 = 0.176$, $F = 60.81$, $P < 0.001$)		
Mean creatinine clearance during treatment	−0.211	0.006
Mean LDL-C	2.426	0.018
Mean HDL-C	−8.797	0.033
Baseline UAE	0.002	0.047

Abbreviations are: HbA_{1c}, glycated hemoglobin; UAE, urinary albumin excretion; β-1/Cr, regression coefficient of yearly plasma creatinine reciprocal after adjustment for baseline values; C_{Cr}, creatinine clearance; LDL-C, low-density lipoprotein cholesterol.

predominant form of the disease, and its prevalence is increasing rapidly, especially in developing countries [24]. There is also evidence suggesting that non-Caucasian type 2 diabetic patients are at increased risk of renal disease relative to Caucasian patients [25, 26]. Hence, type 2 diabetes is the single most important cause of end-stage renal disease worldwide, and its incidence is expected to continue to rise [27, 28]. Although the antiproteinuric effect of ACE inhibitors over other antihypertensive drugs has been repeatedly demonstrated [9], the renoprotective effects of these agents have only been confirmed in type 1 [10] and normotensive type 2 diabetic patients [11, 12].

There is a high prevalence of hypertension, ranging from 30 to 90%, depending on definitions, in type 2 diabetes [29, 30]. Despite the magnitude of this health problem, there are only a few long-term studies, lasting for one year or more, comparing the renal effects of ACE inhibitors with other antihypertensive drugs in hypertensive type 2 diabetic patients [13–15]. In the more recently published studies, results were again inconclusive. In the UKPDS, aggressive control of BP alone was associated with improved clinical outcomes, which were not different between patients treated with captopril and those with atenolol [17]. Other studies have also identified BP, plasma glucose, and lipid levels as the major determinants for the progression of renal function in type 2 diabetic patients [31]. In two recent randomized clinical trials, the advantageous cardioprotective and vasculoprotective effects of ACE inhibitors over calcium channel-blocking agents in these high-risk patients have been confirmed [18, 19]. Although the ABCD trial aimed to examine the renal effects of these treatments, the study failed to reach a conclusion because of its early discontinuation [19]. In patients with chronic renal failure from miscellaneous causes, treatment by ACE inhibition has been shown to attenuate the rate of deterioration of renal function [32–34]. Indeed, in one of these studies, one of the treatment arms had to be discontinued prematurely because of the clear renoprotective effects of ramipril in patients with nondiabetic proteinuria >3 g/day [33]. Despite these encouraging results, in view of the metabolic milieu and multiple medical problems in the majority of type 2 diabetic patients, findings from other patient groups may not necessarily be applicable to the majority of hypertensive type 2 diabetic patients.

ACE inhibition in type 2 diabetic patients

In a three-year study comparing the renal effects of cilazapril and amlodipine, both drugs had similar effects on renal clearance in 44 hypertensive type 2 diabetic patients with or without microalbuminuria [13]. In the recently published ABCD trial that aimed to examine the renal effects of enalapril and nosoldipine in type 2 diabetic patients, the trial had to be discontinued prematurely in the hypertensive arm because of increased mor-

tality and cardiovascular morbidity in the nosoldipine group [19]. In another three-year study comparing the effects of fosinopril and amlodipine in hypertensive type 2 diabetic patients with normoalbuminuria, treatment with fosinopril was associated with a greater reduction in albuminuria and a lower risk of cardiovascular deaths and events compared with amlodipine [18]. However, in all of these relatively short-term studies, the renal protective effects of ACE inhibitors remained inconclusive.

Our cohort is a typical population of type 2 diabetic patients with coexisting hypertension [35, 36]. In keeping with most published studies, approximately 50% of our patients had normoalbuminuria, 25% had microalbuminuria, and 25% had macroalbuminuria. Increasingly unfavorable metabolic profiles, BPs, and renal function were associated with increasing proteinuria [36, 37]. In 1989, when our study was designed and conducted, the primary end point was reduction in UAE, and we found after one year that enalapril treatment was associated with a greater reduction (−54%) in albuminuria than nifedipine (+11%). However, the plasma creatinine increased in both groups and more so in the enalapril-treated patients. The latter rise was probably caused by the rapid fall in BP following the administration of diuretics to the majority of enalapril-treated patients, making the one-year results inconclusive regarding the renoprotective effects of these agents [14]. In the three-year study comparing the renal effects of cilazapril versus amlodipine in type 2 diabetic patients, two phases of progression of renal function were reported. The first phase was a more rapid decline in the glomerular filtration rate (GFR), which was proportional to the magnitude of fall in BP. The second phase represented a slower rate of decline in GFR that was inversely proportional to the fall in BP [13]. A similar pattern was observed in our study, which emphasizes the importance of long-term follow-up in the assessment of renal function.

ACE inhibition and albuminuric status

In this five-year prospective study, the anti-albuminuric effects of enalapril were less marked compared with those reported in the one-year analysis (−13 vs. −54%). Although some of these differences in changes in UAE may represent regressions to the mean, incomplete suppression of plasma angiotensin II levels during chronic ACE inhibitor therapy may also be important [38, 39]. The latter is mainly due to the presence of alternative non-ACE pathways for the conversion of angiotensin I to angiotensin II, such as the chymase pathway [40]. Despite the smaller magnitude of the overall reduction in UAE with prolonged follow-up, patients treated with enalapril, especially those with microalbuminuria, were less likely to progress to macroalbuminuria than the nifedipine group. Against this background, the results of several ongoing long-term prospective randomized studies comparing angiotensin II antagonists and other antihypertensive agents in type 2 diabetic patients with renal impairment are awaited with much interest.

ACE inhibition and progression of renal function

Regarding the progression of renal function, our normoalbuminuric and microalbuminuric patients had similar rates of decline in C_{Cr} once satisfactory BP control had been achieved. Conversely, macroalbuminuric patients showed a substantially greater and relentless deterioration in C_{Cr}, despite similar control of BP. Given the known adverse effects of angiotensin II on renal hemodynamics and tissue growth, as well as the close relationships between albuminuria and progression of renal function in most reports [41], one would expect beneficial effects of ACE inhibitors treatment on renal function in these hypertensive diabetic patients.

However, in this study, there was some discordance between the rate of decline in renal function and the antiproteinuric responses to treatment. At a similar BP control level, progression of renal function was retarded by enalapril in only the macroalbuminuric patients, whereas proteinuria was improved by enalapril in only the microalbuminuric patients. In the macroalbuminuric patients, treatment with enalapril reduced the rate of decline in renal function, expressed as β-1/Cr, although the antiproteinuric effects were less impressive than that in the microalbuminuria group. The latter might be due to the large interindividual and intraindividual variations in UAE among these patients with heavy proteinuria. However, the beneficial effects of ACE inhibitor therapy were easier to detect in these patients in whom renal function tended to decline more rapidly. On the other hand, the improvement in albuminuria observed with enalapril treatment in the microalbuminuric group was not accompanied by a beneficial effect on renal function. Given the relatively long natural history of diabetic proteinuria, the five-year follow-up period might not be sufficiently long enough for these antiproteinuric effects to be translated into renoprotection. However, in spite of the apparent discordance, when the microalbuminuric and macroalbuminuric patients were combined as a group, there was a trend for renal function to stabilize in the enalapril group but deteriorate in the nifedipine group. Because progression of renal function was slow in normoalbuminuric patients, the change in their renal parameters did not reach statistical significance in our study, despite the relatively long mean follow-up period of five years. Nevertheless, when all patients were included in the analysis, more enalapril-treated patients reverted to normoalbuminuria, and fewer of them developed macroalbuminuria compared with the nifedipine-treated patients.

Other points also need to be considered when these

results are interpreted. By chance and despite randomization in a double-blind and placebo-controlled manner, our enalapril-treated patients had a higher mean age and worse lipid profiles than the nifedipine-treated patients at baseline [42]. The enalapril-treated patients were more likely to be treated with diuretics initially and had their antihypertensive therapy changed during the subsequent follow-up. As a result, these enalapril-treated patients did not have as good BP and metabolic control as the nifedipine group. All of these factors might have contributed to the less than expected beneficial effects of ACE inhibitor treatment observed in this study.

Hence, overall, our findings corroborate other studies, which have confirmed the renoprotective effects of ACE inhibitors in patients with nondiabetic renal disease [32–34], as well as in type 1 [10] and normotensive type 2 diabetic patients [11, 12]. However, it is important to note that there was a tendency for renal function to decline more rapidly among our normoalbuminuric patients treated with enalapril compared to the nifedipine group. In this respect, although hypertension and proteinuria frequently coexist in type 1 diabetic patients, many type 2 diabetic patients have hypertension in the absence of proteinuria. Some of these patients may have renovascular disease, and the use of ACE inhibitors may reduce GFR further [27, 43–45]. More studies are required to clarify these diversified responses to antihypertensive treatments in type 2 diabetic patients with different degrees of albuminuria.

Hyperlipidemia and renal function

The pathogenesis of diabetic proteinuria is complex and involves metabolic, hemodynamic, growth, and genetic factors [46]. In this study, apart from albuminuria, renal function was also related to BP, glycemic and lipid indices including serum apo B, LDL-C, triglyceride, and reduced HDL-C concentrations. These findings therefore are in accordance with those in the five-year study of Ravid et al examining the effects of enalapril versus placebo in normotensive type 2 diabetic patients. In these latter patients, changes in albuminuria were also closely associated with changes in lipid indices including reduced HDL-C and increased TC [31, 47].

There is both clinical and experimental evidence demonstrating the relationship between hyperlipidemia and proteinuria. Although treatment with HMG Co-A reductase inhibitors has been shown to reduce proteinuria [48–50], their long-term renal effects remain to be established. Irrespective of these renal interactions, adverse lipid profiles contribute significantly to cardiovascular risk in diabetic patients. After controlling for other variables, both albuminuria and lipid indices were independent predictors for death, cardiovascular events, and renal events in our patients. Thus, the beneficial effects of ACE inhibition on cardiovascular mortality and morbidity [18, 19] may in part be mediated by effects on proteinuria and hyperlipidemia [51, 52]. In the present study, the use of lipid-lowering drugs was similar between the enalapril and nifedipine group. Although the macroalbuminuric patients had the highest frequency of clinical endpoints, we were unable to show a superior effect of enalapril over nifedipine in reducing these events.

Glycemic control and renal function

In the present study, glycemic control, including fasting plasma glucose and HbA_{1c}, was also an important determinant of the progression of renal function, along with age, male gender, and lipid indices. The beneficial effects of optimal glycemic control on microvascular complications, including proteinuria, have been shown in type 1 [6] and type 2 diabetic patients [7, 53]. In a separate cohort analysis, our group has previously shown that the mortality rate of our type 2 diabetic patients was 3% per year, mainly due to cardiovascular events or renal failure. Fasting plasma glucose and albuminuria were the independent predictors of death [54]. There is increasing evidence indicating direct toxic effects of hyperglycemia on cellular functions. These include activation of the sorbitol pathway [55] and alteration of intracellular signaling pathways, such as increased expression of protein kinase C leading to endothelial dysfunction, activation of cytokines and disturbed cellular growth [56]. These factors, together with the frequent coexistence of other risk factors such as hypertension, obesity, and hyperlipidemia, may all contribute to the increased mortality and morbidity, as well as deterioration of renal function in type 2 diabetic patients [1].

CONCLUSION

In this prospective cohort analysis involving 102 hypertensive type 2 diabetic patients with varying degrees of albuminuria followed for a mean duration of five years, we have observed the importance of good metabolic and BP control regarding the progression of albuminuria and renal function. Patients with macroalbuminuria had the worst clinical outcomes, including cardiovascular events, as well as an accelerated deterioration in renal function. Treatment with enalapril was associated with a greater reduction in albuminuria than nifedipine, especially in the microalbuminuric patients. In the macroalbuminuric patients, the rate of deterioration in renal function was also attenuated by treatment with enalapril.

Reprint requests to Juliana C.N. Chan, M.D., Department of Medicine and Therapeutics, Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong.
E-mail: jchan@cuhk.edu.hk

REFERENCES

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors and 12-year cardiovascular mortality for men

screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
2. Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA: Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *Br Med J* 294:1443–1447, 1987
3. Fuller JH, Stevens LK, Wang SL: International variations in cardiovascular mortality associated with diabetes mellitus: The WHO Multinational Study of Vascular Disease in Diabetes. *Ann Med* 28:319–322, 1996
4. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G, the Scandinavian Simvastatin Survival Study (4S) Group: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20:614–620, 1997
5. Kuusisto J, Mykkanen L, Pyorala K: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
6. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
7. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with NIDDM: A randomised prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
8. Hostetter TH: Mechanisms of diabetic nephropathy. *Am J Kidney Dis* 23:188–192, 1994
9. Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF: Effect of antihypertensive therapy on the kidney in patients with diabetes: A meta-regression analysis. *Ann Intern Med* 118:129–138, 1993
10. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456–1462, 1993
11. Ravid M, Lang R, Bachmani R, Lishner M: Long term renoprotective effect of angiotensin converting enzyme inhibition in non-insulin dependent diabetes mellitus: A 7 year follow up study. *Arch Intern Med* 156:286–289, 1996
12. Ahmad J, Siddiqui MA, Ahmad H: Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 20:1576–1581, 1997
13. Velussi M, Brocco E, Frigato F, Zolli M, Muollo B, Maioli M, Carraro A, Tonolo G, Fresu P, Cernigoi AM, Fioretto P, Nosadini R: Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. *Diabetes* 45:216–222, 1996
14. Chan JCN, Cockram CS, Nicholls MG, Cheung CK, Swaminathan R: Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: One year analysis. *Br Med J* 305:981–985, 1992
15. Melbourne Diabetic Nephropathy Study Group: Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. *Br Med J* 302:210–216, 1991
16. UKPDS: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 8). *Br Med J* 317:703–713, 1998
17. UKPDS: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 39). *Br Med J* 317:713–720, 1998
18. Tatti P, Pahor M, Byington R, Mauro PD, Guarisco R, Strolol G, Strollo F: Outcome results of the fosinopril versus amlodipine cardiovascular events randomised trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 21:597–603, 1998
19. Raymond OE, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW: The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with NIDDM and hypertension. *N Engl J Med* 338:645–652, 1998
20. World Health Organisation: *Diabetes mellitus: Report of a WHO Study group* (Technical reports series 727). Geneva, World Health Organisation, 1985, p 11
21. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
22. Cheung CK, Swaminathan R: Rapid, economical immunoturbidimetric method for albuminuria. *Clin Chem* 33:204–205, 1987
23. Mogensen CE, Vestbo E, Poulsen PL, Christiansen C, Damsgaard EM, Eiskjær H, Frøland A, Hansen KW, Nielsen S, Pedersen MM: Microalbuminuria and potential confounders. *Diabetes Care* 18:572–581, 1995
24. *The World Health Report 1997:* Conquering suffering, enriching humanity. Geneva, World Health Organisation, 1997
25. Allawi J, Rao PV, Gilbert R, Scott G, Jarrett RJ, Keen H, Viberti GC, Mather HM: Microalbuminuria in non-insulin-dependent diabetes: Its prevalence in Indian compared with Europoid patients. *Br Med J* 296:462–464, 1988
26. Young RP, Chan JCN, Poon E, Critchley JAJH, Cockram CS: Associations between albuminuria and angiotensinogen T235 and angiotensin converting enzyme deletion polymorphims in Chinese NIDDM patients. *Diabetes Care* 21:431–437, 1997
27. Ritz E, Nowack R, Fliser D, Koch M, Tschope W: Type II diabetes mellitus: Is the renal risk adequately appreciated. *Nephrol Dial Transplant* 6:679–682, 1991
28. Cowie CC, Port FK, Wolfe RA: Disparities in incidence of diabetes end stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–1079, 1989
29. DeFronzo RA, Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
30. Parving H-H: Renal protection in diabetes: An emerging role for calcium antagonists. *J Hypertens* 14(Suppl 4):S21–S25, 1996
31. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R: Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure and hyperglycaemia. *Arch Intern Medicine* 158:998–1004, 1998
32. Maschio G, Alberti D, Janin G, Locatelli F, Mann J, Morolese M, Ponticelli C, Ritz E, Zucchelli P: Effect of the angiotensin converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334:939–945, 1996
33. The GISEN Group: Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in porteinuric, non-diabetic nephropathy. *Lancet* 349:1857–1863, 1997
34. Hannedouche T, Landais P, Goldfarb B, Esper NE, Fournier A, Godin M, Durand D, Chanard J, Mignon F, Suc J-M, Grunfeld J-P: Randomised controlled trial of enalapril and beta blockers in non diabetic chronic renal failure. *Br Med J* 309:833–837, 1994
35. The Hypertension and Diabetes Study Group: Hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens* 11:309–317, 1993
36. Chan JCN, Cheung CK, Swaminathan R, Nicholls MG, Cockram CS: Obesity, albuminuria and hypertension among Hong Kong Chinese with non-insulin-dependent diabetes mellitus (NIDDM). *Postgrad Med J* 69:204–210, 1993
37. Dinneen SF, Gerstein HC: The association of microalbuminuria and mortality in NIDDM. *Arch Intern Med* 257:1413–1418, 1997
38. Biollaz J, Brunner HR, Gavras I, Waeber B, Gavras H: Antihypertensive therapy with MK-421: Angiotensin II renin relationships to evaluate efficacy of converting enzyme blockade. *J Cardiovasc Pharmacol* 4:966–972, 1982
39. Mento PF, Wilkes BM: Plasma angiotensins and blood pressure during converting enzyme inhibition. *Hypertension* 9(6 Pt 2; Suppl III): III42–III48, 1987
40. Urata H, Kinoshita A, Misono KS, Bumpus FM, Husain A: Identification of a highly specific chymase as the major angiotensin II forming enzyme in the human heart. *J Biol Chem* 265:22348–22357, 1990
41. Rossing P, Hommel E, Smidt UM, Parving HH: Reduction in albuminuria predicts diminished progression in diabetic nephropathy. *Kidney Int* 45(Suppl):145–149, 1994
42. Chan JCN, Nicholls MG, Cheung CK, Law LK, Swaminathan

R, Cockram CS: Factors determining the blood pressure response to enalapril and nifedipine in hypertension associated with NIDDM. *Diabetes Care* 18:1001–1006, 1995
43. Sawicki PT, Kaiser S, Heinemann L, Frenzel H, Berger M: Prevalence of renal artery stenosis in diabetes mellitus: An autopsy study. *J Intern Med* 229:489–492, 1991
44. Selby JV, Fitzsimmons SC, Newman JM, Katz PP, Sepe S, Showstack J: The natural history of epidemiology of diabetic nephropathy: Implication for prevention and control. *JAMA* 263:1945–1960, 1990
45. Valvo E, Bedogna V, Casagrande P, Antiga L, Zamboni M, Bommartini F, Oldrizzi L, Rugiu C, Maschio G: Captopril in patients with type II diabetes and renal insufficiency: Systemic and renal hemodynamic alterations. *Am J Med* 85:344–348, 1988
46. Parving H-H, Tarnow L, Rossing P: The angiotensin-converting enzyme gene and its inhibition in diabetic nephropathy. *Curr Opin Endocrinol Diabetes* 3:315–321, 1996
47. Ravid M, Neumann L, Lishner N: Plasma lipids and the progression of nephropathy in diabetes mellitus type II: Effect of ACE inhibitors. *Am J Kidney Dis* 47:907–910, 1995
48. Lam KS, Cheng IKP, Janus ED, Pang RWC: Cholesterol lowering therapy is may retard the progression of diabetic nephropathy. *Diabetologia* 38:604–609, 1995
49. Kasiske BL, Cleary MP, O'Donnell MP, Keane WF: Effects of genetic obesity on renal structure and function in Zucker rat. *J Lab Clin Invest* 106:598–604, 1985
50. Kasiske BL, O'Donnell MP, Cleary MP, Keane WF: Treatment of hyperlipidaemia reduces glomerular injury in obese Zucker rats. *Kidney Int* 33:667–672, 1988
51. Keilani T, Schlueter W, Levin ML, Batlle DC: Improvement of lipid abnormalities associated with proteinuria using fosinopril, an angiotensin converting enzyme inhibitor. *Ann Intern Med* 18:246–254, 1993
52. Chan JCN, Yeung VTF, Leung DHY, Tomlinson B, Nicholls MG, Cockram CS: The effects of enalapril and nifedipine on carbohydrate and lipid metabolism in NIDDM. *Diabetes Care* 17:859–862, 1994
53. UKPDS: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
54. Chan JCN, Cheung CK, Cheung MYF, Swaminathan R, Critchley JAJH, Cockram CS: Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM. *Diabetes Care* 18:1013–1014, 1995
55. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. *Diabetes Care* 13:610–630, 1990
56. Koya D, King GL: Protein kinase C activation and the development of diabetic complications. *Diabetes* 47:859–866, 1998