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ORIGINAL ARTICLE

Aggressive antihypertensive therapy based on hydrochlorothiazide, candesartan or lisinopril as initial choice in hypertensive type II diabetic individuals: effects on albumin excretion, endothelial function and inflammation in a double-blind, randomized clinical trial

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We investigated the effects of aggressive antihypertensive therapy based on hydrochlorothiazide, candesartan or lisinopril on urinary albumin excretion, endothelial function and inflammatory activity in hypertensive type II diabetic individuals. A total of 70 hypertensive type II diabetic individuals were treated with three antihypertensive strategies in a randomized, double-blind, double-dummy design. Blood pressure was titrated to levels below 130/85 mmHg or a decrease in systolic pressure of 10% with a diastolic pressure below 85 mmHg. After titration, patients were treated for 12 months. Mean blood pressures changed from 157/93, 151/94 and 149/93 at baseline to 135/80, 135/82 and 131/80 mmHg after titration in the hydrochlorothiazide ($n=24$), candesartan ($n=24$) and lisinopril ($n=22$) groups. About 70% reached target blood pressures. However, only 45% had blood pressures $<130/85$ mmHg. Urinary albumin excretion and levels of soluble vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 decreased (GEE regression coefficients, -2.40 mg/24 h ($P<0.001$), -85 ng/ml ($P=0.01$) and -50 ng/ml ($P=0.02$)), but brachial artery endothelium-dependent and -independent vasodilation and levels of von Willebrand factor and C-reactive protein did not change (GEE regression coefficients, 0.21 mm ($P=0.07$), 0.04 mm ($P=0.43$), 0.04 IU/ml ($P=0.33$) and -1.15 mg/l ($P=0.64$)). No differences in outcome variables *between* treatment groups were observed. These data show that achievement of target blood pressures below 130/85 mmHg in hypertensive type II diabetes is difficult. Aggressive antihypertensive therapy can improve urinary albumin excretion, endothelial function and inflammatory activity in hypertensive type II diabetic individuals, regardless of the type of antihypertensive therapy used.

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Introduction

Hypertensive type II diabetic individuals are at high risk of cardiovascular disease. Strict blood pressure control has been shown to improve cardiovascular prognosis in type II diabetes.[1] In addition, recent

studies[2,3] have suggested that angiotensin type 1 (AT_1) receptor antagonists or angiotensin-converting enzyme (ACE) inhibitors may have beneficial effects on the development of diabetic complications beyond their blood-pressure-lowering effects. Although both AT_1 receptor antagonists and ACE-inhibitors act on the renin–angiotensin system, the mechanisms responsible for their effects may be different. Both these concepts, however, remain controversial and the observed differences between antihypertensive drugs may instead be attributable to differences in achieved blood pressures.[4] Current guidelines for treatment of hypertension in type II diabetes recommend lowering blood pressure to below 130/80 mmHg.[5] To achieve this, aggressive drug therapy is often needed. Therefore, blood-pressure-independent effects of AT_1 receptor antagonists or ACE-inhibitors are of clinical relevance only if they remain present given the use of aggressive drug therapy. Comparison of these drugs with conventional (ie, diuretic-based) treatment as initial therapy in the context of aggressive antihypertensive strategy is thus important.

The mechanisms responsible for the beneficial effects of antihypertensive agents on diabetic complications are incompletely understood. Endothelial dysfunction and chronic low-grade inflammation[6] have been shown to be associated with the development of diabetic complications. Several studies have shown that antihypertensive therapies can improve endothelial function and inflammatory activity.[7–10] However, the effect of aggressive antihypertensive treatment on endothelial function and inflammation in type II diabetes is unknown. In addition, it is unknown whether aggressive antihypertensive therapy based on different classes of antihypertensive drugs has differential effects on these processes (see also Table 1).

In view of these considerations, we investigated (1) the effects of aggressive antihypertensive therapy based on hydrochlorothiazide, candesartan or lisinopril on urinary albumin excretion, endothelial function and inflammatory activity in relatively uncomplicated hypertensive type II diabetic individuals; and (2) whether there were differences between the therapies based on these drugs.

Subjects and methods

Between July 1998 and October 2001, a randomized double-blind, double dummy, intervention study of patients with type II diabetes mellitus and hypertension was performed in the outpatient clinic of the VU University Medical Center, Amsterdam, and five other hospitals in the same region. The goal of the study was to investigate the effects of aggressive antihypertensive treatment based on hydrochlorothiazide, candesartan or lisinopril on left ventricular mass and arterial stiffness (as primary outcomes), and on other cardiovascular risk factors (as secondary outcomes). This study describes the effects on the *secondary end points*, urinary albumin excretion, endothelial function and inflammatory activity.

Subjects

Patients were recruited from the Internal Medicine outpatient clinics and by newspaper advertise-

Table 1 Current knowledge on the effects of strict blood pressure control on kidney function, endothelial function and inflammation in type II diabetes

Current knowledge on
Strict blood pressure control
- Strict blood pressure control has been shown to improve cardiovascular prognosis[1]
- Strict blood pressure control has been shown to improve microvascular prognosis[21]

Effects of different classes of antihypertensive drugs on kidney function
- AT1 receptor anatogists have been shown to have a beneficial effect on kidney function[2,22,23]
- ACE-inhibitors have been shown to have a beneficial effect on kidney function[24]

Effects of different classes of antihypertensive drugs on endothelial function
- Only short-term studies (4–12 weeks of antihypertensive treatment)[7-10]
- Only one study in type II diabetes showed that an ACE-inhibitor could decrease sVCAM-1, not sICAM-1[8]
- Only one study showed no change in sVCAM-1 levels after hydrochlorothiazide treatment for 4 weeks[7]
- AT1 receptor antagonists were shown to improve endothelial function in the elderly[9]
- AT1 receptor antagonists were shown to improve or have no effect on endothelial function in hypertensive individuals[7,10]
- ACE-inhibitor can improve endothelial function in hypertensive individuals[10]

Effects of different classes of antihypertensive drugs on inflammation
- ACE-inhibitors have no effect on ICAM-1 levels in type II diabetes[8] and can improve ICAM-1 levels in hypertensive individuals[10]
- AT1 receptor antagonists can either improve or have no effect on sICAM-1 levels[9,10]

What knowledge does this paper add
The effect of *strict* blood pressure control on kidney function, endothelial function and inflammation in type II diabetes
Head-to-head comparison of three main classes of antihypertensive drugs

ments. Inclusion criteria for the run-in period were type II diabetes mellitus for $\geqslant 6$ months (WHO criteria 1985), age between 35 and 70 years, Caucasian ethnicity, and urinary albumin excretion < 100 mg/24 h. Individuals were excluded in case of pregnancy or planning pregnancy, a history of myocardial infarction, angina pectoris, coronary artery bypass surgery, angioplasty, stroke, congestive heart failure, malignancy or other serious illnesses, serum creatinine $>140\,\mu$mol/l, body mass index >35 kg/m^2, alcohol and/or drug abuse, or participation in other clinical trials. The protocol was approved by the appropriate medical ethics committees.

Study protocol

The study consisted of three periods: the 1-month run-in period, the 4 to 6-month blood pressure titration period and the actual 12-month study period (Figure 1). Eligible patients entered into a run-in period on a 100 mmol/24 h sodium containing diet without antihypertensive medication. When patients used ACE-inhibitors, these were withdrawn for 3 months, before patients entered the run-in period. Patients with a sitting blood pressure above 140/90 mmHg and below 190/120 mmHg after the run-in period had an echocardiography. Patients were included if left ventricular mass index was >90 g/m^2 in men or >70 g/m^2 in women. The patients were then randomised to receive once daily treatment with 12.5 mg hydrochlorothiazide, 8 mg candesartan or 10 mg lisinopril, according to a randomization list. In order to maintain a double-blind character throughout the study each patient received, besides the allocated intervention, placebo tablets for the other two study medications. We aimed to achieve a sitting blood pressure below 130/85 mmHg, or a sitting systolic blood pressure decrease of more than 10% combined with a sitting diastolic blood pressure below 85 mmHg. When target pressure was not reached the following steps were added consecutively: 12.5 mg hydrochlorothiazide; doubling of study medication; 5 mg felodipine; 50 mg metoprolol; 2 mg doxazosin; 5 mg felodipine; 50 mg metoprolol; 2 mg doxazosin; 5 mg felodipine; 100 mg metoprolol; and 4 mg doxazosin (when contraindications were present or side effects occurred relevant steps were skipped). The 12-month study phase started when target blood pressures had been achieved or, if not, when the end of the titration schedule had been reached.

We did echocardiography, assessments of vascular function, laboratory assessments, blood pressure and pulse rate measurements at baseline, and after 6 and 12 months of treatment. We measured blood pressure after 5 min of seated rest (mean of three consecutive measurements).

24-h Ambulatory blood pressure

Ambulatory blood pressure was measured as previously described.[11]

Urinary albumin excretion

Urinary albumin excretion (mg/24 h) was determined as the mean of three 24 h urine collections at baseline and after 12 months of treatment, and of one collection at 6 months of treatment. Microalbuminuria was defined as a urinary albumin excretion >30 mg/24 h and <300 mg/24 h.

Endothelial function

Endothelium-dependent, flow-mediated vasodilation and endothelium-independent, nitroglycerin-induced vasodilation were assessed as described in detail elsewhere.[12,13] Concentrations of markers of endothelial function were assessed in deep frozen (-70°C) plasma samples. Von Willebrand factor (vWf) antigen levels was measured as previously described.[14] Soluble (s) vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) were estimated using commercially available ELISA kits (Diaclone, Besançon, France).

Inflammatory activity

C-reactive protein (CRP) was measured with a highly sensitive in-house ELISA.[15] We considered sICAM-1 to be both an estimate of endothelial function and an estimate of inflammatory activity.

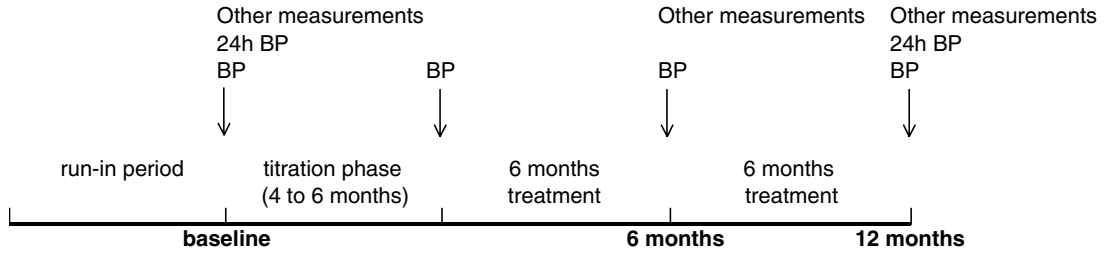

Figure 1 Time points of measurements during the study. Other measurements were urinary albumin excretion, endothelium-(in)dependent vasodilation, levels of vWf, sVCAM-1, sICAM-1 and CRP. BP, blood pressure.

Levels of sVCAM-1, sICAM-1 and CRP were determined only in those who completed follow-up ($n = 60$).

Statistical analyses

The sample size calculation was based on the primary outcome variables of this study (left ventricular mass and carotid artery distensibility). Therefore, and due to a lack of information on the effect of hydrochlorothiazide treatment on our secondary outcomes (urinary albumin excretion, endothelial function and inflammatory activity), formal power calculations were not performed for the secondary outcome variables presented here. However, the power of our results is shown by the 95% confidence intervals of the between-groups comparisons in Table 3 and 4 (see Results; ie, a wide interval is an indication of low power). We used generalized estimating equation (GEE) analyses[16] to investigate the development in urinary albumin excretion, endothelial function and inflammatory activity over time in the whole group. Values at 6 and 12 months (adjusted for the 6-month-value) were used as outcome. For endothelium-(in)dependent vasodilation, we used the maximal diameter after ischaemia or nitroglycerin as outcome variable corrected for the basal diameter. To investigate whether the development over time for a particular variable was dependent on the blood pressure decrease, we adjusted for systolic blood pressure in additional models. Next, we investigated whether the changes in urinary albumin excretion were mediated by changes in endothelial function or inflammatory activity, and whether changes of endothelial function and inflammatory activity were mediated by each other. Finally, we investigated differences between the three treatment groups.

A two-tailed $P < 0.05$ was accepted as the level of significance. Statistical analyses were performed with SPSS 9.0. GEE analyses were performed with STATA (version 7).

Results

A total of 70 individuals were included in the study and 60 completed the entire study period. Figure 2 shows a CONSORT flow diagram of the individuals through each stage of the study. One patient in the hydrochlorothiazide and one in the lisinopril group received additional amiloride treatment because potassium levels were < 3.5 mmol/l. None of the patients included used nitrates. Individuals who discontinued the study were not different in baseline characteristics from those who continued, except that they had higher triglyceride levels (data not shown). Table 2 shows the clinical characteristics at baseline. No differences in baseline clinical

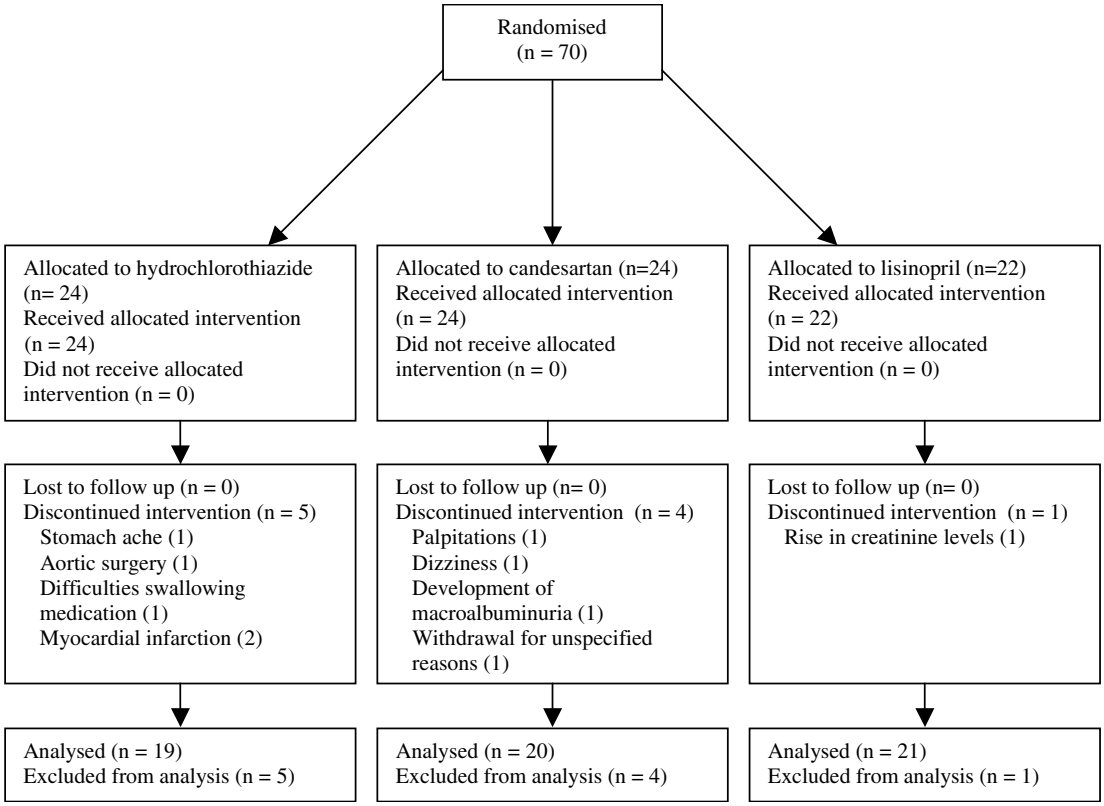

Figure 2 CONSORT flow diagram. Individuals who discontinued did that before (nine), or directly after the 6-month measurement (one).

Table 2 Baseline clinical characteristics of hypertensive type II diabetic individuals

	Hydrochlorothiazide (n = *24*)	*Candesartan* (n = *24*)	*Lisinopril* (n = *22*)
Age (years)	63±6	60±7	62±8
Sex (men/women)	16/8	13/11	14/8
Fasting glucose (mmol/l)	8.3±2.4	8.3±1.7	7.2±2.1
HbAlc (%)	7.6±1.4	7.2±1.2	7.2±1.2
Systolic blood pressure (mmHg)	157±13	151±14	149±9
Diastolic blood pressure (mmHg)	93±9	94±10	93±7
Body mass index (kg/m^2)	29.5±3.5	28.8±3.7	29.0±4.3
Current smoking (yes/no)	5/19	5/18[a]	4/18
Total cholesterol (mmol/l)	5.2±1.2	5.4±1.0	5.2±1.0
LDL-cholesterol (mmol/l)	2.8±0.9[b]	3.2±0.9	3.2±0.9
HDL-cholesterol (mmol/l)	1.3±0.6	1.2±0.7	1.3±0.4
Triglycerides (mmol/l)	1.7 (1.3–2.5)	1.8 (1.2–2.6)	1.4 (1.1–2.2)
Plasma creatinine (μmol/l)	95±11	91±13	95±19
Creatinine clearance (Cockroft-Gault) (ml/min)	94±16	101±24	96±27
Left ventricular mass (g/m^2)	115.3±23.5	115.0±24.0	114.9±26.6
Urinary albumin excretion (mg/24 h)	12.4 (7.0–22.7)	12.3 (7.7–20.5)	13.2 (7.3–32.0)
Normoalbuminuria/microalbuminuria	18/4	18/3	14/7
Endothelium-dependent vasodilation (mm)	0.21±0.19	0.26±0.25	0.37±0.22
Endothelium-independent vasodilation (mm)	0.50±0.32	0.44±0.22	0.49±0.30
vWf (IU/ml)	1.60±0.51	1.61±0.49	1.61±0.53
sVCAM-1 (ng/ml)	785±182	899±340	805±308
sICAM-1 (ng/ml)	570±154	638±223	598±196
CRP (mg/l)	1.74 (1.07–3.18)	1.97 (1.14–3.65)	2.17 (1.65–5.85)

[a]Data on one individual were missing.
[b]Data on LDL cholesterol were missing in two individuals in the hydrochlorothiazide group due to triglyceride levels above 5.0 mmol/l.

characteristics between the treatment groups were observed, except that systolic blood pressure was slightly higher in the hydrochlorothiazide group. Levels of HbA1c and lipids did not change significantly during the study period (data not shown).

Effects of aggressive antihypertensive therapy

In total, 69% achieved the blood pressure goals after the titration phase, with the median use of three antihypertensive drugs. In all, 45% reached pressures below 130/85 mmHg, 45% reached a systolic pressure below 130 mmHg and 87% reached a diastolic pressure below 85 mmHg. Both sitting systolic and diastolic blood pressures decreased significantly between baseline and 6 and 12 months (Table 3). Levels of urinary albumin excretion, sVCAM-1 and sICAM-1 decreased significantly after 6 and 12 months of treatment compared to baseline, while endothelium-(in)dependent vasodilation, levels of vWf and CRP did not change significantly over time (Table 3). Adjustment for changes in systolic blood pressure did not materially change these results.

Comparison of the effects of hydrochlorothiazide-, candesartan- and lisinopril-based strategies

In total, 75, 67 and 68% achieved the blood pressure goals after the titration phase, with the median use of four, three and three antihypertensive drugs in the hydrochlorothiazide (daily median dose, 25 mg), candesartan (16 mg) and lisinopril groups (20 mg), respectively. Both sitting systolic and diastolic blood pressures decreased significantly between baseline and 6 and 12 months in all treatment groups, while no differences between treatment groups were observed. Mean±s.d. systolic and diastolic pressures in the hydrochlorothiazide, candesartan and lisinopril groups were 157±13/93±9, 151±14/94±10 and 149±9/93±7 mmHg at baseline, 135±13/80±9, 135±15/82±8 and 131±10/80±4 mmHg after the titration phase, 136±13/82±8, 134±15/83±10 and 135±13/79±6 mmHg after 6 months of treatment, and 137±12/82±8, 133±15/81±11 and 132±12/80±7 mmHg after 12 months of treatment, respectively. Results were similar for the 24-h blood pressure measurements. Mean±s.d. 24-h systolic and diastolic pressures were 140±15/83±7, 136±12/79±8 and 136±13/81±9 mmHg at baseline in the hydrochlorothiazide, candesartan and lisinopril groups, and decreased to 131±15/77±7, 128±13/76±9 and 126±15/73±7 mmHg after 12 months of treatment.

No differences in development over time of urinary albumin excretion, vWf, sVCAM-1, sICAM-1 and CRP were observed between treatment groups. However, as compared to hydrochlorothiazide-based treatment, candesartan-based treatment was associated with an increased endothelium-dependent vasodilation ($P = 0.024$; Table 4 and Figure 3).

Table 3 Effects of aggressive antihypertensive therapy on blood pressure, urinary albumin excretion, endothelial function and inflammatory activity

	GEE regression coefficient (6 months)	*95% CI*	*GEE regression coefficient (12 months)*	*95% CI*
Systolic blood pressure (mmHg)	−17.7	−21.0 to −14.4	−18.3	−21.3 to −15.2
Diastolic blood pressure (mmHg)	−11.7	−13.6 to −9.8	−12.1	−14.0 to −10.1
Urinary albumin excretion (mg/24 h)[a]	−1.91	−2.57 to −1.38	−2.40	−3.16 to −1.82
Endothelium-dependent vasodilation (mm)	0.15	−0.07 to 0.36	0.21	−0.02 to 0.44
Endothelium-independent vasodilation (mm)	0.04	−0.04 to 0.12	0.04	−0.06 to 0.13
vWf (IU/ml)	0.04	−0.05 to 0.01	0.04	−0.04 to 0.01
sVCAM-1 (ng/ml)	−100	−150 to −50	−85	−150 to −20
sICAM-1 (ng/ml)	−55	−88 to −22	−50	−93 to −6
CRP (mg/l)[a]	−1.41	−2.40 to 1.23	−1.15	−2.04 to 1.55

Results are expressed as regression coefficients and 95% confidence intervals (95% CI) obtained with GEE analyses. A regression coefficient of −17.7 (top left) means that systolic blood pressure decreased with 17.7 mmHg between baseline and 6 months of treatment.
[a]Urinary albumin excretion and CRP were log-transformed because of their skewed distribution in analyses; regression coefficients were back-transformed.

Table 4 Differences between treatments: candesartan and lisinopril *vs* hydrochlorothiazide

	GEE regression coefficient	*95% CI*
Candesartan minus hydrochlorothiazide		
Systolic blood pressure (mmHg)	−3.3	−11.6 to 5.0
Diastolic blood pressure (mmHg)	−0.5	−3.1 to 2.1
Urinary albumin excretion (mg/24 h)[a]	1.03	−1.14 to 1.21
Endothelium-dependent vasodilation (mm)	0.099	0.013 to 0.184
Endothelium-independent vasodilation (mm)	0.108	−0.027 to 0.243
vWf (IU/ml)	0.03	−0.07 to 0.01
sVCAM-1 (ng/ml)	−2.6	−77.3 to 72.0
sICAM-1 (ng/ml)	26.8	−23.9 to 77.5
CRP (mg/l)[a]	1.48	−1.66 to 3.63
Lisinopril minus hydrochlorothiazide		
Systolic blood pressure (mmHg)	−3.6	−11.0 to 3.8
Diastolic blood pressure (mmHg)	−1.3	−3.5 to 0.9
Urinary albumin excretion (mg/24 h)[a]	1.05	−1.12 to 1.24
Endothelium-dependent vasodilation (mm)	0.037	−0.069 to 0.143
Endothelium-independent vasodilation (mm)	0.073	−0.060 to 0.206
vWf (IU/ml)	0.00	−0.01 to 0.01
sVCAM-1 (ng/ml)	2.4	−76.1 to 80.9
sICAM-1 (ng/ml)	−23.1	−67.0 to 20.9
CRP (mg/l)[a]	−1.23	−2.69 to 1.78

Results are expressed as regression coefficients and 95% confidence interval (95% CI) obtained with GEE analyses. A regression coefficient of −3.3 means that systolic blood pressure was 3.3 mmHg lower in the candesartan than in the hydrochlorothiazide group. Regression coefficients of the difference between candesartan and lisinopril can be calculated by subtracting the regression coefficients of candesartan and lisinopril as shown in this table.
[a]Urinary albumin excretion and CRP were log-transformed because of their skewed distribution; regression coefficients were back-transformed.

In the whole group, the decrease in urinary albumin excretion was partially (∼30%) dependent on the decrease in systolic pressure (data not shown); this was ∼70% in the hydrochlorothiazide and candesartan groups, and ∼5% in the lisinopril group. The decrease in urinary albumin excretion was independent of changes in endothelial function and inflammatory activity (data not shown).

In the whole group, the decreases in sVCAM-1 and sICAM-1 were mutually related, and ∼20 and ∼0% dependent on the decrease in systolic blood pressure (data not shown). This was ∼90 and ∼50% in the hydrochlorothiazide group *vs* ∼0% in the candesartan and lisinopril groups.

Discussion

This study shows that, by using aggressive antihypertensive therapy, about 70% of our hypertensive type II diabetic population achieved target blood pressures. Aggressive blood-pressure-lowering therapy was associated with beneficial effects on kidney and endothelial function, and on inflammatory activity. However, we could not demonstrate significant differences in effects of the antihypertensive strategies based on hydrochlorothiazide, candesartan or lisinopril, which may be due to the small sample size of this study.

Despite strict antihypertensive strategies and intensive guidance of the study participants, only 70% reached blood pressure targets and only 45% reached a systolic pressure below 130 mmHg, suggesting that treatment of hypertension in type II diabetes is difficult. In addition, 65% needed at least three antihypertensive drugs to achieve these pressures. International guidelines on type II diabetes[5] recommend even lower blood pressure goals (130/80 mmHg), but such goals will be difficult to achieve.

Our results suggest that, among relatively uncomplicated hypertensive type II diabetic patients with normoalbuminuria or early microalbuminuria, aggressive antihypertensive treatment decreases urinary albumin excretion, improves some aspects of

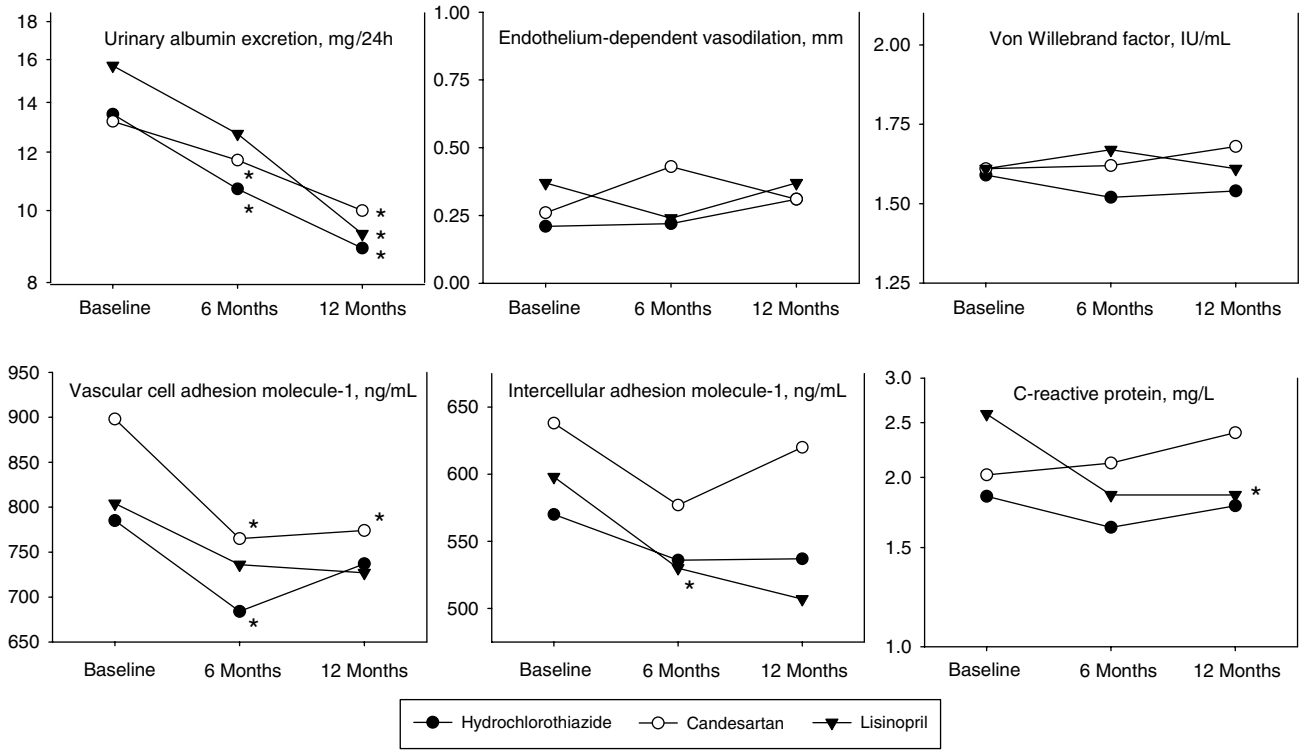

Figure 3 Urinary albumin excretion, endothelium-dependent vasodilation, vWf, sVCAM-1, sICAM-1 and CRP in the hydrochlorothiazide, candesartan and lisinopril groups. $^*P<0.05$ *vs* baseline. Owing to the skewed distributions of urinary albumin excretion and CRP the data for these variables are shown on a log scale.

endothelial function, and decreases inflammatory activity.

Increases in urinary albumin excretion signify progression of early nephropathy and, in addition, are strongly associated with risk of cardiovascular disease.[17] Therefore, the decrease in urinary albumin excretion obtained with aggressive antihypertensive therapy, although small, may be clinically important. The decrease in urinary albumin excretion was similar in all three groups. Overall, about one-third was mediated by the decrease in systolic blood pressure. Aggressive antihypertensive treatment was associated with decreases in the levels of sVCAM-1 and sICAM-1. High adhesion molecule levels[6] are associated with increased cardiovascular risk in type II diabetes, presumably because such high levels reflect endothelial dysfunction (sVCAM-1 and sICAM-1) as well as chronic, low-grade vascular inflammation (sICAM-1). Therefore, decreases in these markers may confer a decrease in cardiovascular risk, although prospective data are needed to test this hypothesis. The decreases in sVCAM-1 and sICAM-1 were similar in all three groups and did not clearly depend on the blood pressure decrease, except in the hydrochlorothiazide group. These data suggest that sVCAM-1 and sICAM-1 levels can be lowered both by decreasing blood pressure and by inhibiting the effects of angiotensin II, but that these effects are not additive at the blood pressures achieved in this study. Indeed, experimental work has shown that the activity of the transcription factor NF-κB, which regulates gene expression of several endothelial cell adhesion molecules, including sVCAM-1 and sICAM-1, can be decreased both by decreasing blood pressure and by blocking the effects of angiotensin II.[18] However, due to the relatively small sample size of our study, these observations should be interpreted with caution.

Beneficial effects of AT_1 receptor blockade and ACE inhibition on urinary albumin excretion and sVCAM-1 have been reported previously.[2,7–10] We found only one study that evaluated the effect of hydrochlorothiazide; it showed no effect on endothelial function.[7] However, these studies did not use strict blood pressure targets.

Aggressive antihypertensive treatment was associated with a small increase in brachial artery flow-mediated, endothelium-dependent vasodilation (Table 3). Impaired endothelium-dependent vasodilation is thought to be associated with increased cardiovascular risk, presumably because it reflects decreased availability of nitric oxide and other vasoactive mediators. The increase in endothelium-dependent vasodilation was blood-pressure-independent and was somewhat greater in the candesartan and lisinopril groups than in the hydrochlorothiazide group. These data show that

impaired flow-mediated vasodilation in hypertensive type II diabetic patients is only modestly responsive to aggressive antihypertensive treatment. The causes of this unresponsiveness are unclear and require further investigation.

Aggressive antihypertensive treatment was not associated with decreased levels of vWF and CRP. Both markers are strongly associated with risk of cardiovascular disease.[19,20] The present data suggest that other factors, such as hyperglycaemia, advanced glycation end products and adipocytokines may be more important determinants of vWF and CRP than high blood pressure.

Our study had several limitations. Most importantly, the groups were small, and we may have missed differences between the hydrochlorothiazide-, candesartan- and lisinopril-based treatments, as illustrated by the confidence limits of the results shown in Table 4. Therefore, the observations presented here should be interpreted with caution. However, differences between therapies, if any, are likely to be relatively small, especially in relatively uncomplicated type II diabetic patients. Secondly, because of the variability of office blood pressures, we may have underestimated the effect of the blood pressure decrease on the outcome measures. Third, concentrations of plasma markers of endothelial function and inflammation were only measured once, which might have diluted the associations we found, which thus may to some extent have been underestimated. In addition, because urinary albumin excretion, endothelial dysfunction and low-grade inflammation in type II diabetes tend to increase with time,[6] we probably have underestimated the (beneficial) effects of aggressive antihypertensive treatment on these variables.

In conclusion, aggressive antihypertensive treatment based on hydrochlorothiazide, candesartan or lisinopril, although difficult, can improve kidney and endothelial function, and inflammatory activity in relatively uncomplicated hypertensive type II diabetic individuals. The clinical significance of such improvements, however, remains to be demonstrated.

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