# Irbesartan Reduces the Albumin Excretion Rate in Microalbuminuric Type 2 Diabetic Patients Independently of Hypertension

## A randomized double-blind placebo-controlled crossover study

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**OBJECTIVE** — ACE inhibitors delay the progression from incipient to overt diabetic nephropathy and reduce albumin excretion rate (AER), independently of blood pressure. Angiotensin II type 1 receptor antagonists produce similar effects on microalbuminuria and mean arterial pressure. The aim of this study was to evaluate the effect of irbesartan on microalbuminuria and blood pressure in hypertensive and normotensive type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — Sixty-four microalbuminuric hypertensive (group 1) and 60 microalbuminuric normotensive (group 2) type 2 diabetic male patients, matched for age, BMI, $HbA_{1c}$, and diabetes duration, were enrolled. Each group was divided into two subgroups receiving either irbesartan (150 mg b.i.d. orally) or placebo for 60 days. After 15 days of washout, irbesartan was given to the subgroups who had received the placebo, and vice versa, in a randomized double-blind crossover study.

**RESULTS** — In microalbuminuric hypertensive type 2 diabetic subjects, irbesartan reduced 24-h mean systolic and diastolic pressure and AER. In microalbuminuric normotensive type 2 diabetic patients, irbesartan reduced AER.

**CONCLUSIONS** — These results indicate the beneficial effects of irbesartan on AER in type 2 diabetic subjects, independently of its antihypertensive effects.

*Diabetes Care* 25:1909–1913, 2002

Diabetic nephropathy is the most common cause of renal failure in western society. Numerous factors predispose diabetic subjects to the development of renal disease. Hypertension is a major risk factor, and there is a direct correlation between glycemic control and the impairment of renal function (1). Thus, strategies for preventing the progression of renal failure in diabetic patients, particularly in the early phase of nephropathy, include blood pressure (BP) as well as glycemic control (2). Diabetic nephropathy develops gradually and slowly, finally leading to overt disease. The first indication of diabetic nephropathy is microalbuminuria, i.e., albumin excretion rate (AER) between 20 and 200 μg/min, in at least two of three consecutive measurements. This condition is referred to as "incipient nephropathy." In both type 1 and type 2 diabetes, microalbuminuria is a predictor of persistent proteinuria and early death from cardiovascular disease (3).

The renin angiotensin system (RAS) is considered to be a paracrine regulator of renal function and blood flow, thus playing an important role in the progression of chronic renal disease, as seen in diabetic nephropathy. The effects of blocking the RAS with ACE inhibitors on delay or prevention of incipient to overt nephropathy and renal failure are widely recognized (4).

Experimental studies and clinical trials have demonstrated that ACE inhibitors lower microalbuminuria independently of BP control (5,6); thus, blocking RAS with ACE inhibitors is beneficial for hypertensive as well as normotensive microalbuminuric diabetic patients.

ACE inhibitors are more effective than conventional antihypertensive agents because they can modify both systemic and local pressure. However, ACE inhibitors also act on systems other than RAS, resulting in side effects, such as cough and angioneurotic edema, that reduce patient compliance.

Blocking angiotensin II receptors with the angiotensin type 1 receptor antagonist ($AT_1$-RA) inhibits angiotensin more directly than ACE inhibitors (7). By not interfering with any metabolic process in RAS, this different action mechanism may account for the excellent tolerability observed with the angiotensin II receptor antagonists.

Head-on comparison of equipotent doses of ACE inhibitors and angiotensin II receptor blockers in hypertensive nondiabetic patients produces equal reductions in mean arterial pressure and proteinuria (8,9). Recently, some clinical trials dem-

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Received for publication 2 March 2002 and accepted in revised form 15 July 2002.

**Abbreviations:** AER, albumin excretion rate; $AT_1$-RA, angiotensin type 1 receptor antagonist; $AT_2$, angiotensin type 2; BP, blood pressure; RAS, renin angiotensin system.

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

**Table 1—*Baseline characteristics of the randomized subjects***

| | Hypertensive | | Normotensive | |
|---|---|---|---|---|
| | Subgroup 1 | Subgroup 2 | Subgroup 1 | Subgroup 2 |
| *n* | 32 | 32 | 30 | 30 |
| Age (years) | 49.2 ± 4.3 | 48.6 ± 2.5 | 49.0 ± 4.1 | 47.6 ± 4.4 |
| BMI (kg/m$^2$) | 26.7 ± 1.4 | 26.1 ± 0.6 | 25.7 ± 1.7 | 25.7 ± 1.2 |
| $HbA_{1c}$ (%) | 7.4 ± 0.6 | 7.6 ± 0.6 | 7.5 ± 0.4 | 7.5 ± 0.3 |
| Serum potassium (mmol/l) | 4.5 ± 0.4 | 4.2 ± 0.3 | 4.4 ± 0.3 | 4.3 ± 0.3 |
| Diabetes duration (years) | 4.4 ± 1.8 | 5.2 ± 2.8 | 4.9 ± 1.8 | 5.3 ± 1.4 |
| 24-h mean systolic BP (mmHg) | 161 ± 12 | 159 ± 10 | 128 ± 8 | 125 ± 7 |
| 24-h mean diastolic BP (mmHg) | 96 ± 6 | 96 ± 5 | 81 ± 5 | 82 ± 4 |
| AER (μg/min) | 120 ± 35 | 123 ± 28 | 101 ± 30 | 112 ± 32 |

Data are *n* or means ± SD.

onstrated the effectiveness of $AT_1$-RA in reducing AER in patients with hypertension, microalbuminuria, and type 2 diabetes (10,11). Microalbuminuria can affect diabetic patients before the onset of hypertension. However, the possibility of slowing the progression of AER also in normotensive type 2 diabetic patients with microalbuminuria has not yet been tested. The aim of this study was to evaluate the effect of irbesartan, an angiotensin II receptor blocker, on microalbuminuria in normotensive and hypertensive type 2 diabetic patients.

## RESEARCH DESIGN AND METHODS

### Subjects and study protocol

The study was approved by the ethics committee of the Second University of Naples, Naples, Italy. All subjects were seen at the outpatient clinic of metabolic disease and recruited over 3 months.

A total of 80 hypertensive and 79 normotensive (BP <140/90 mmHg) microalbuminuric type 2 diabetic male subjects with nonproliferative diabetic retinopathy, in good metabolic control with oral hypoglycemic agents as judged by $HbA_{1c}$ levels, were initially studied. Hypertensive patients had newly diagnosed mild-to-moderate essential hypertension (diastolic BP ≥90 mmHg and <110 mmHg, systolic BP ≥140 and <180 mmHg), and they had not received antihypertensive treatment. All patients were screened for AER (assessed from overnight urine, three times during the last 6 months) and 24-h ambulatory BP monitoring with every half-hour measurement, according to the Holter method (manufactured by Welch Allyn/Tycos, Arden, NC). Patients with a history of nondiabetic renal disease, renal failure (creatinine clearance <80 ml/min and/or serum creatinine ≥106 mmol/l [1.2 mg/dl]), urinary tract infections, serum potassium >5.0 mmol/l, electrocardiogram signs, symptoms or history of heart disease, acute or severe chronic liver disease, and autonomic neuropathy (assessed by the heart rate responses to deep breathing, to Valsalva maneuver, and to standing and by the BP response to standing, according to age-related normal ranges) were excluded. A total of 16 hypertensive and 15 normotensive diabetic patients were not randomized because they were macroalbuminuric (AER >200 μg/min) at least in one of the three overnight urine collections. Moreover, four patients in the normotensive group were not randomized because they showed impaired levels of BP (>10% of measurements higher than 140 and 90 mmHg, respectively, for systolic and diastolic values during 24-h ambulatory BP monitoring).

After written informed consent was obtained, 64 hypertensive type 2 diabetic subjects with microalbuminuria (group 1) and 60 normotensive type 2 diabetic subjects with microalbuminuria (group 2), matched for age, BMI, $HbA_{1c}$, and diabetes duration, were enrolled (Table 1). The subjects followed a randomized double-blind placebo-controlled crossover protocol, with the primary end point being AER. The secondary end point was a change in systolic and diastolic BP.

After 15 days of run-in with placebo, patients were randomized to either irbesartan (subgroup 1, 150 mg b.i.d. orally) or placebo (subgroup 2) and entered a treatment period of 60 days (period 1). After 15 days of washout, the patients were crossed over to the alternate regimen for another 60 days (period 2). At the end of run-in (time 0), at the end of period 1 (time 1), at the end of wash-out (time W), and at the end of period 2 (time 2), AER, $HbA_{1c}$, serum potassium, and 24-h ambulatory BP monitoring were re-evaluated in each subject (Fig. 1). On each of the last 3 days of run-in, period 1, wash-out, and period 2, a 24-h urine collection was performed; thus, AER was assessed in terms of the mean of these values. Ambulatory BP was measured every 2 weeks by the same expert physician from the beginning of run-in until the end of the study.

During the study, patients followed a normocaloric diet (30 kcal/kg) with an ordinary sodium level (~150 mmol/day) and a constant amount of protein (1.2 g·kg body wt$^{-1}$·day$^{-1}$). Lifestyle and oral hypoglycemic therapy remained unchanged throughout the study. Patients were dropped out if one of the following events occurred: macroalbuminuria, serum po-

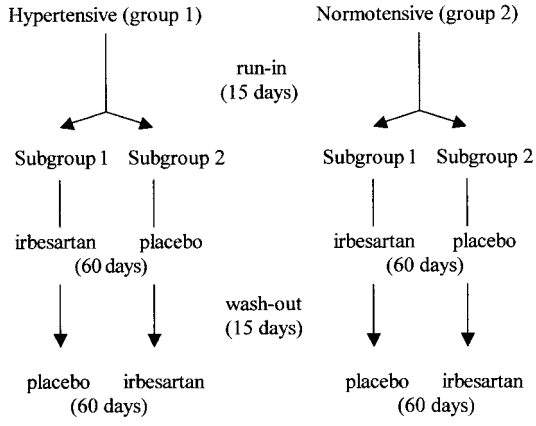


**Figure 1—*Study design. Normotensive and hypertensive groups were divided into two subgroups (subgroup 1: irbesartan first; subgroup 2: placebo first) according to a cross-over study.***

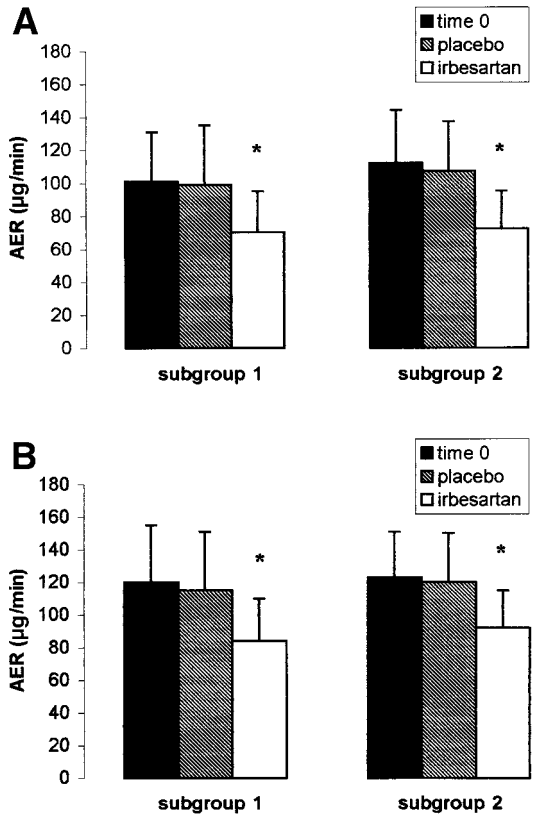


**Figure 2—***AER in the two subgroups of normotensive* (A) *and hypertensive* (B) *diabetic subjects.* *P < *0.01.*

tassium >5.0 mmol/l, ambulatory systolic BP <100 mmHg, and/or diastolic BP <60 mmHg. The investigations were performed in accordance with the principles of the Declaration of Helsinki.

$HbA_{1c}$ was determined by column chromatography using a commercial kit (Bio-Rad); reference levels were 4–6%, and the interassay coefficient of variation was 3%. AER was analyzed by immunoturbidimetric method (DCA 2000 Analyzer; Bayer, München, Germany), the interassay coefficient of variation was 4.1%, and the lowest detection limit was 5 µg/ml.

### Statistical analysis

The null hypothesis was that the results in the placebo and the irbesartan groups would be equal after 60 days of treatment. Assuming a difference in decreased proportions of 25%, the null hypothesis had a 90% power with a 0.05 significance level. Within-treatment analysis (post-treatment end point compared with baseline) and between-treatment analysis (compared with placebo) were performed using ANOVA with covariance adjustment. The dependent variable was the change from baseline. Medication (placebo or irbesartan) was treated as a repeated measure. Order of treatment (placebo first or irbesartan first) was a grouping factor. A $P$ value <0.05 was considered significant. All statistical analyses were done using SPSS 8.0 for Windows (SPSS, Chicago). Data in the text and tables are expressed as means ± SD.

## RESULTS

— Of the 159 patients who entered the study, 124 were randomized (Table 1). AER was significantly reduced ($P < 0.01$) at the end of irbesartan treatment in both hypertensive (mean change from baseline in subgroup 1, irbesartan −36 µg/min, placebo −5 µg/min, and in subgroup 2, irbesartan −35 µg/min, placebo −3 µg/min) and normotensive (mean change from baseline in subgroup 1, irbesartan −31 µg/min, placebo −2 µg/min, and in subgroup 2, irbesartan −40 µg/min, placebo −5 µg/min) diabetic patients (Fig. 2).

The 24-h mean systolic BP was significantly reduced ($P < 0.01$) at the end of irbesartan treatment in hypertensive (mean change from baseline in subgroup 1, irbesartan −15 mmHg, placebo −1 mmHg, and in subgroup 2, irbesartan −12 mmHg, placebo −2 mmHg) but not in normotensive (mean change from baseline in subgroup 1, irbesartan −6 mmHg, placebo −3 mmHg, and in subgroup 2, irbesartan −1 mmHg, placebo −3 mmHg) diabetic patients. Similar results were obtained from the analysis of 24-h mean diastolic BP in hypertensive (mean change from baseline in subgroup 1, irbesartan −6 mmHg, placebo −1 mmHg, and in subgroup 2, irbesartan −7 mmHg, placebo −1 mmHg; $P < 0.01$) and normotensive (mean change from baseline in subgroup 1, irbesartan −1 mmHg, placebo −1 mmHg, and in subgroup 2, irbesartan −1 mmHg, placebo 0 mmHg) diabetic patients.

The falls in AER and BP for the two arms of the trial were similar in each group, and no order effect was observed. In both groups, $HbA_{1c}$ and serum potassium were not significantly modified during the study.

Both irbesartan and placebo were well tolerated. Of the 124 randomized patients, 27 (22%) reported adverse reactions. Adverse events were mild and reported by less patients on placebo (11%) compared with irbesartan (14.5%). Five patients (4%) experienced adverse events during both placebo and irbesartan treatments. The more frequent adverse events were respiratory infections and headache. Hypoglycemia and nausea were less frequent. However, all randomized patients completed the trial.

## CONCLUSIONS

— The progression of renal disease correlates with arterial hypertension and proteinuria. Thus, many studies have been performed to establish the effect of pharmacological treatment on these disorders. It is recommended that arterial pressure be maintained lower in diabetic patients than in nondiabetic patients (12). Many drug regimens have been evaluated and compared, such as calcium-channel blockers, cardioselective β-blockers, diuretics, and ACE inhibitors. All are effective antihypertensive agents and delay the decline of renal function in diabetic patients with persistent proteinuria. ACE inhibitors seem to be preferred (13), and angiotensin II inhibition may be the most effective therapy for both targets (14,15).

ACE inhibitors delay the progression

of diabetic nephropathy by reducing BP and improving the altered renal hemodynamics of diabetic subjects (16). Angiotensin II, in fact, vasoconstricts the efferent more than the afferent arterioles, thus enhancing glomerular pressure and altering permeability. In diabetic animals, glomerular efferent arteriole tone is increased (17). The higher urinary excretion of albumin correlates not only with systemic pressure, but mostly with glomerular pressure. In experimental diabetic nephropathy, ACE inhibitors prevent the rise in AER and the glomerular ultrastructural changes (increased glomerular basement membrane thickness and glomerular and total mesangial volume) (18).

Selective blockade of the angiotensin II type 1 receptor is a novel mechanism for interrupting RAS. $AT_1$-RA has been shown to be comparable to ACE inhibitors in lowering arterial BP and microalbuminuria (8,9), with the beneficial effect of blocking angiotensin II generated by non–angiotensin-converting enzyme pathways and without altering either bradykinin metabolism or the potential beneficial effects of angiotensin type 2 ($AT_2$) receptor stimulation. In fact, blocking either ACE or the $AT_1$ receptors enhances renin secretion; the first induces an increase in angiotensin I, and the second induces increased angiotensin II, leading to increased $AT_2$ receptor activation. There is growing evidence that $AT_2$ receptor stimulation may be beneficial to the cardiovascular system. Many authors place particular emphasis on the nonhemodynamic properties of angiotensin II as a renal growth factor. The majority of mechanisms for angiotensin II are attributed to $AT_1$ receptors, but also $AT_2$ receptors are present in the kidneys (19). Different from $AT_1$, $AT_2$ receptor stimulation causes vasodilatation, inhibits cell proliferation, and promotes cell differentiation through production of bradykinin, nitric oxide, and cGMP (20–23). In patients with diabetic nephropathy, mRNA $AT_1$ receptor expression is low in both tubules and glomeruli (24). This result may reflect a regulatory response to inappropriately high intrarenal angiotensin II concentrations and action.

$AT_1$-RAs operate a specific blockade of $AT_1$, thus increasing angiotensin II concentration and overstimulating $AT_2$ receptors. As a result of their double antiproliferative effect, both direct $AT_1$ receptor–mediated and indirect $AT_2$ receptor–mediated $AT_1$-RAs could protect against mesangial expansion. However, the molecular mechanisms in the pathogenesis of renal injury, as well as the angiotensin II receptor subtype involvement, are not fully identified. Therefore, further investigations have to be performed to explain more clearly the positive action of irbesartan observed in our patients.

Irbesartan is a long-acting $AT_1$-RA with a dose-related action and a good tolerability profile. This makes it a promising therapeutic approach to diabetes management (25). In experimental type 2 diabetes, irbesartan was effective against hypertension and renal injury (26). Very recently, two randomized double-blind placebo-controlled clinical trials demonstrated that irbesartan is renoprotective independently of its blood pressure–lowering effect in hypertensive patients with type 2 diabetes. In the irbesartan diabetic nephropathy trial (27), irbesartan was effective in protecting against the progression of nephropathy due to type 2 diabetes, lowering both the risk of doubling the serum creatinine concentration and the relative risk of end-stage renal disease. In the IRbesartan MicroAlbuminuric type 2 diabetes in hypertensive patients (IRMA II) study (10), irbesartan was protective against the onset of persistent albuminuria (AER $>$200 μg/min) in hypertensive patients with type 2 diabetes and microalbuminuria. However, the effectiveness of irbesartan on lowering AER in normotensive microalbuminuric type 2 diabetic patients was tested only in one study with a small number of patients (27).

This study was designed as a short-term trial. However, the reduction in AER observed after 2 months with irbesartan treatment is in accordance with the findings shown in the IRMA II after 3 months of therapy (~30% for both studies), proving the quick nephroprotective action of irbesartan.

In the current study, newly diagnosed drug-naive hypertensive patients were investigated, whereas the above-mentioned trials studied exclusively (10), or for almost 95% (27), previously diagnosed patients who had their antihypertensive medications washed out. Thus, although a small cohort in absolute terms, the sample size in the current study is considerable. Moreover, the previous trials used sitting BP, whereas in the current study, the better method of ambulatory BP monitoring was performed.

In conditions where RAS plays a key role in the control of renal hemodynamics and proliferation, such as diabetic nephropathy, a more complete inhibition can be achieved by combining angiotensin II antagonists and ACE inhibitors.

There are several potential benefits of combined treatment with ACE inhibitors and $AT_1$-RA in a patient with renal disease: enhanced blockade of RAS (e.g., an increase in plasma renin activity), no change or slight reduction in plasma aldosterone levels, increased renal plasma flow, preserved glomerular filtration rate, reduced proteinuria, and suppressed cytokine expression (e.g., tumor growth factor $\beta_1$) (28,29).

These findings suggest that $AT_1$-RA treatment in the early stages of diabetic nephropathy is effective in avoiding side effects from ACE inhibitors and modulating angiotensin II effects. This is possible because $AT_1$-RA operate through two different mechanisms: synthetic and receptorial.

In agreement with previous observations, in this study, irbesartan reduces microalbuminuria in hypertensive type 2 diabetic patients. Moreover, it has been originally observed that an $AT_1$-RA reduces microalbuminuria even in normotensive type 2 diabetic patients.

These findings show that, like ACE inhibitors, the nephroprotective action of irbesartan is unrelated to its antihypertensive effect. Moreover, irbesartan seems to decrease AER even in a prehypertensive phase. These data suggest that the reduction of intraglomerular pressure, and probably a more favorable balance between activation of $AT_1$ and $AT_2$ receptors in mesangial cells, may favorably act in retarding the progression of renal impairment, also when hypertension does not already aggravate diabetic nephropathy.

The effect of irbesartan on microalbuminuria, even in normotensive type 2 diabetic subjects, suggests that the nephroprotection brought about by $AT_1$-RA could be caused by the direct action on renal hemodynamics and glomerular morphology.

Finally, in light of current evidence derived from large clinical trials, this study suggests that irbesartan, and probably other $AT_1$-RAs, may have a role in

primary prevention of diabetic nephropathy.

**Acknowledgments**— The authors thank Joseph Sepe, MD, for revising the text.

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